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VOL. 35, NO. 6 JUNE, 1961

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AMERICAN COLLEGE
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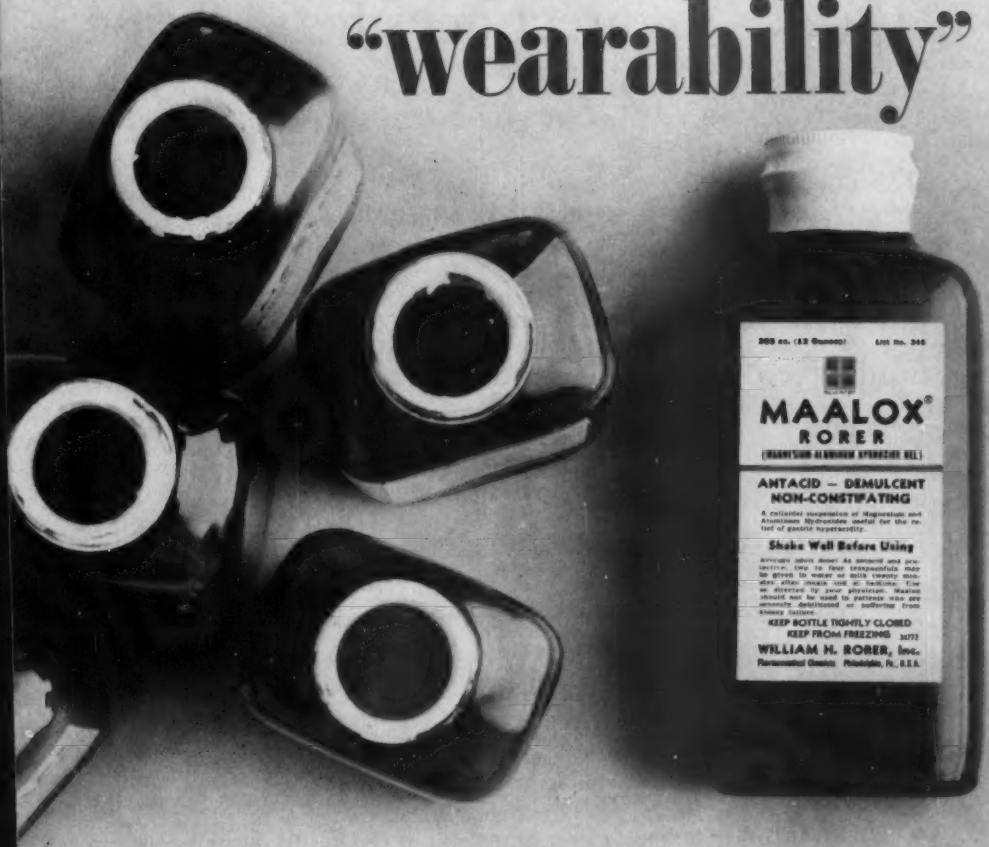

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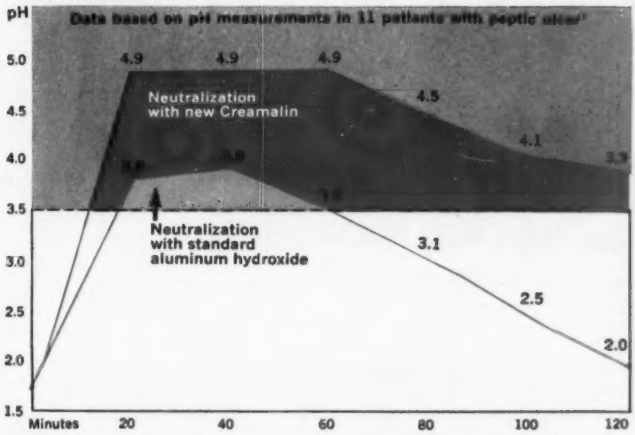

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1. Data in the files of the Department of Medical Research, Winthrop Laboratories. 2. Hinkel, E. T., Jr.; Fisher, M. P., and Tainter, M. L.: J. Am. Pharm. A. (Scient. Ed.) 48:384, July, 1959.

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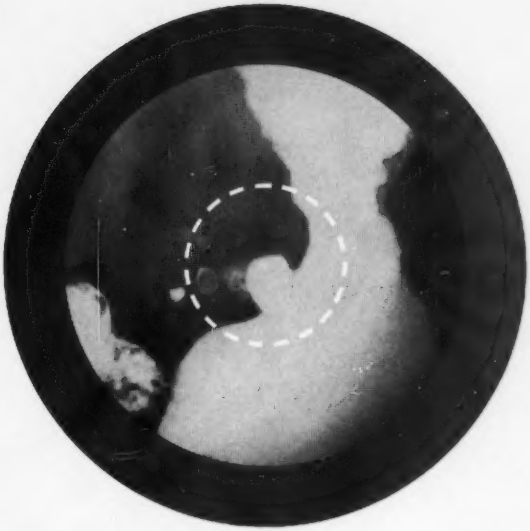

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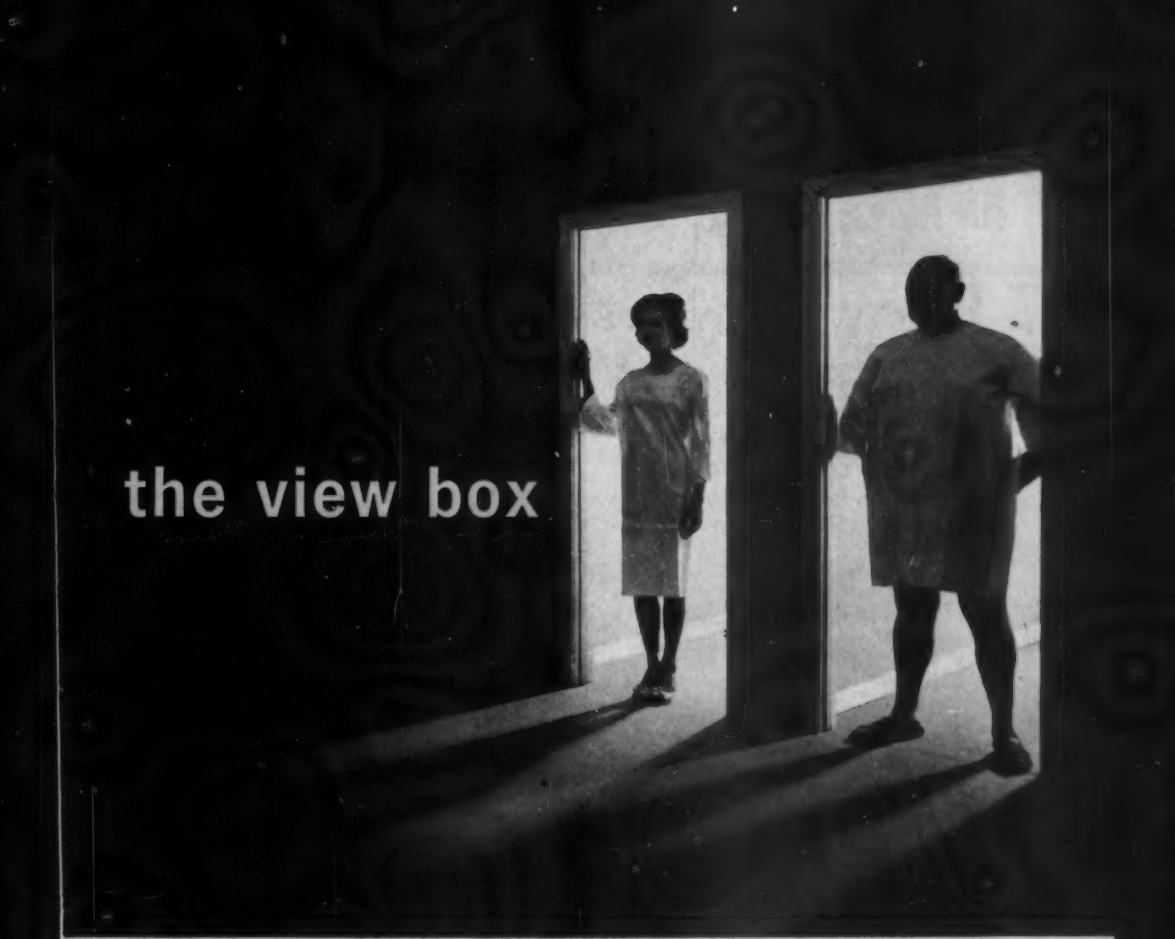

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Bibliography

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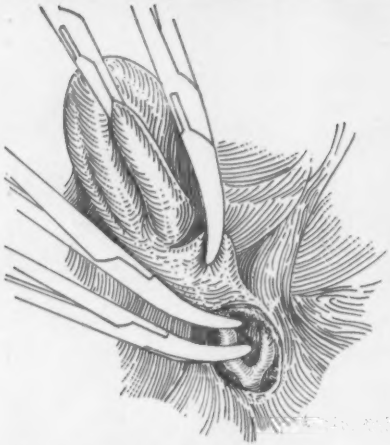

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Source: **Farris, J. M., and Smith, G. K.: M. Clin. North America *43*:1133 (July) 1959.**

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IDIOPATHIC NONTROPICAL SPRUE (MALABSORPTION SYNDROME)*

ERIC E. WOLLAEGER, M.D.

and

PAUL A. GREEN, M.D.

Rochester, Minn.

Diseases of the small intestine that are characterized by impaired absorption of multiple nutrients eventually lead to a clinical state called the sprue syndrome. The essential features of this syndrome are the signs and symptoms of abnormal intestinal function, such as diarrhea, flatulence and loss of weight, plus the manifestations of associated nutritional-deficiency states that are usually present, such as anemia, hypoproteinemia with edema, and osteomalacia. Primary or idiopathic sprue, which includes tropical and nontropical sprue in adults and celiac disease in infants and children, is a chronic disease of unknown cause that lacks specific gross pathologic changes, though characteristic microscopic abnormalities of the mucosa of the small intestine have been demonstrated[1-6]. Primary sprue must be distinguished from sprue syndromes secondary to other diseases that interfere with function of the small intestine such as regional enteritis, Whipple's disease, tumors of the small intestine, and resections or short-circuiting anastomoses of that organ (Table I).

Although long considered to be a disease limited to tropical or subtropical climates, sprue has been recognized in the temperate zones of Europe and North America with increasing frequency during the last half century[7-14]. The syndrome as observed in temperate climates is in most respects similar to that seen in the tropics, though certain differences have been noted[13]. It is possible, as some observers believe, that tropical and nontropical sprue are the same disease occurring in different climatic belts of the world[10,11]. If not identical, they may at least stem from the same basic defect which has been influenced by different environmental factors such as climate, infection or diet[13-15]. There is good evi-

*Read before the 25th Annual Convention of the American College of Gastroenterology, Philadelphia, Pa., 24, 25, 26 October 1960.

From the Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minn.

dence to support the widely held belief that nontropical sprue in adults and celiac disease in infants and children are manifestations of the same disease[5].

Nontropical sprue has frequently been called "idiopathic steatorrhea" and more recently it has been designated "malabsorption syndrome". We prefer the term "nontropical sprue" because of its close resemblance to (if not identity with) tropical sprue and because in our experience it is a specific disease entity[13,16]. The term "idiopathic steatorrhea" emphasizes one of the outstanding clinical features of the disease, namely the presence of excessive quantities of fat in the feces. The use of this term, however, ignores the fact that the impairment of absorption affects all nutrients, including proteins, carbohydrates, vitamins, minerals and even water[13,17,18]. Furthermore, there are other disease states characterized by steatorrhea of unknown cause which cannot rightly be classified with this group[19]. The term "malabsorption syndrome" would seem to include all diseases in which abnormalities of absorption exist. Among these would be many diseases having no close relationship or resemblance to sprue such as hemochromatosis, Wilson's disease, sarcoidosis and pernicious anemia. From the standpoint of accurate diagnosis and proper treatment little is to be gained by grouping all such diseases together under the single term "malabsorption syndrome".

In our experience, primary or idiopathic nontropical sprue is the form of the sprue syndrome most frequently encountered. This disease is not uncommon as evidenced by the fact that the diagnosis was made at the Mayo Clinic 261 times during the 10-year period 1945 through 1954. From this number we selected for detailed study 124 cases in which the duration of the disease had been 5 years or longer. By this means of selection and with the clinical laboratory and roentgenologic data that were available, we believed that we were able to eliminate from the series all cases of the sprue syndrome secondary to other diseases. A detailed report of the clinical findings in this group of cases has been published elsewhere[16]. Steatorrhea existed in every case, and in all but five its presence was demonstrated by means of quantitative fecal-excretion studies conducted over a period of 1 to 6 days.

Pathology

The patients in this series were studied prior to the introduction of methods for biopsy of the mucosa of the small intestine, and therefore the demonstration of pathologic changes played no part in their selection. Subsequently, however, we have obtained biopsy specimens from a number of these patients and in every instance some degree of the characteristic mucosal changes of sprue has been demonstrated. The experience of some investigators has led them to believe that these abnormalities may be specific for sprue and celiac disease and are not found in other conditions[5,20]. If such results are confirmed by a wider experience in the examination of jejunal biopsy material from patients with a variety

of clinical disorders, intubation biopsy will no doubt become the single most important method for establishing the diagnosis of sprue. It has not yet been clearly demonstrated, however, that all patients with sprue exhibit the characteristic mucosal changes, particularly those with mild disease or disease of recent onset.

The outstanding microscopic abnormality in sprue and celiac is the blunting, flattening, decrease in size or even complete disappearance of the villi in the duodenum and jejunum, which has the effect of diminishing the absorptive surface of this segment of the bowel to a considerable degree[5]. Microscopic

TABLE I

CLASSIFICATION OF SPRUE SYNDROMES

Primary sprue
Nontropical
Tropical
Celiac disease
Secondary sprue
Regional enteritis
Amyloidosis
Scleroderma
Whipple's disease
Lymphoma and other neoplasms of small intestine or its mesentery
Chronic external pancreatic insufficiency
Surgical resections and short circuits of small intestine
Enteroenteric fistulas
Diabetes mellitus with neuropathy
Diverticula, blind loops and strictures of small intestine
Tuberculosis of small intestine or mesenteric lymph nodes

changes in the individual columnar cells covering the villi have also been described, including flattening of the cells, abnormalities in the cytoplasm and nucleus and abnormalities of the microvilli covering their free surface[2,6]. The microvilli may be deficient in size or number or both, but such changes have not been demonstrable in all cases of sprue[20].

INCIDENCE AND CLINICAL FINDINGS

In our series of cases[16], nontropical sprue was found to be a little more than twice as common in women as in men. The onset of symptoms occurred at almost any age but was rare after the age of 60. In a fairly high proportion of cases (11 per cent) the disease started in infancy and early childhood. No doubt

these represented cases of celiac disease that persisted into adult life. In about two-thirds of the cases in the series, the disease began between the ages of 20 and 50 years.

The chronic nature of sprue was indicated by our finding that the average duration of the disease from the time of onset until the time that we obtained our most recent follow-up information was 19 years, with a range from 5 to 64 years. The disease often had a very insidious onset with intermittent episodes of mild diarrhea, weakness and loss of weight, or with a chronic unexplained anemia. In other cases the onset was much more abrupt, with an episode of severe diarrhea. Rarely, the only presenting complaint was bone pain from osteomalacia with little or no antecedent history of diarrhea or other symptoms of disturbed intestinal function[21,22].

We found the disease to be characterized by remissions, which occurred either spontaneously or as the result of treatment[16]. Only five patients in the series had experienced no remissions, and the maximal duration of remissions in the remaining patients varied from a few months to 10 years or longer, in most cases ranging from 6 months to 3 years.

The most frequent and prominent symptoms were weakness, diarrhea and loss of weight. Flatulence, glossitis, stomatitis, crampy abdominal distress and dyspepsia were common, but severe and persistent abdominal pain was rare. The appearance of the stools during episodes of diarrhea did not always suggest the presence of steatorrhea since they were often described as watery rather than greasy. Most of the patients in the series, however, gave a history of having observed pale, bulky, fatty stools typical of steatorrhea during the exacerbations of their illness. Twelve patients were unable to recall any significant episodes of diarrhea and a few complained of constipation. The high incidence of Vitamin D deficiency and osteomalacia in this group of patients was indicated by the fact that 40 per cent of them had experienced tetany and many also had suffered from bone pains. Gross hemorrhages due to Vitamin K deficiency occurred in about one-fourth of the patients in the series, while edema of the lower extremities associated with hypoproteinemia was noted during the course of the disease by approximately half of them.

Obvious loss of weight and muscular wasting constituted the most prominent physical sign. The mean height of patients in the series, however, was fairly normal for their sex. Of interest is the fact that a large proportion of the patients had been underweight continuously throughout their adult life and possibly during their entire lifetime. This was true despite the fact that in most cases the symptoms of sprue did not begin till long after the patient had reached adulthood. The maximal lifetime weight attained by 63 per cent of the patients in the series was either below normal or in the low-normal range (within 5 pounds of the lowest standard weight with respect to the patient's height for

the individual of small body frame*). Body weight had been above normal in only 8 per cent of the cases.

Aside from loss of weight the most frequent abnormal physical finding was abdominal distention, followed closely in frequency by edema of the lower extremities. Melanosis of the skin, arterial hypotension and clubbing of the fingers were relatively common findings. Fever occurred in only a few cases, and was usually due to intercurrent infection. Neuropathy of any sort was rare.

Laboratory studies demonstrated a high incidence of anemia and macrocytosis, each of which occurred in about 60 per cent of the cases. The incidence and degree of anemia would no doubt have been considerably increased if many of these patients had not been treated with various hematopoietic agents prior to examination. Reduction in concentration of serum protein occurred both in the albumin and globulin fractions and was sometimes marked. One patient was found to have agammaglobulinemia of the acquired type[23]. Chemical evidence of osteomalacia (with abnormally low values for serum calcium, serum phosphate or both) was present in 77 patients, and a similar number were found to be deficient in prothrombin. A flat glucose-tolerance curve was observed in more than 90 per cent of the patients tested, and a so-called deficiency pattern of the small intestine was demonstrated roentgenologically in 94 per cent of the 109 patients examined by this method. Measurement of the concentration of carotene in the serum did not always result in a diagnostically low value since this was less than 40 international units per 100 c.c. in only 15 of the 20 patients tested. Its value as a screening procedure for the diagnosis of sprue must therefore be considered to have some limitations[24].

Since impaired absorption of fat is probably the most constant and characteristic feature of any form of sprue, we have considered that the diagnosis must be based upon demonstration of this abnormality. Measurement of fat absorption has been attempted in various ways, including microscopic examination of the feces, determination of blood level and tolerance of fat and fat-soluble vitamins such as carotene and Vitamin A, and determination of plasma and fecal radioactivity following ingestion of triolein tagged with radioactive iodine. None of these methods have proved to be sufficiently accurate to replace the more arduous method of collecting and analyzing for fat all feces excreted over a period of 1 to several days in order to arrive at the quantity of fat excreted per 24 hours[25,26]. In our experience, analysis of a single stool specimen to determine the percentage of fecal solids comprised by fat indicates the presence of steatorrhea when elevated values are obtained, but normal values do not exclude its presence. In testing for steatorrhea we found it advantageous to carry out both types of analysis (fat excretion per 24 hours and per cent of fecal solids comprised by fat) on the fecal collections of patients being tested[16]. Many of these

*Metropolitan Life Insurance Tables.

collections were made while the patient was taking a test diet containing 100 gm. of fat per day[27], though in other instances the patient took his usual diet containing less fat than this. A value for fecal fat exceeding 7.5 gm. per day or a concentration exceeding 30 per cent of total fecal solids was considered to confirm the existence of steatorrhea. Collection of feces over a period of at least 72 hours was considered desirable, but oftentimes if the patient was having many stools per day this period was shortened to 48 hours or even to 24. Excretion of fecal fat in our series varied from values only slightly above the normal range to 87 gm. per day, the average being 25.7 gm. per day. That microscopic examination of the feces is not an entirely reliable screening procedure is demonstrated by the fact that no excess of fat was noted in 19 of 104 patients who were shown by quantitative chemical methods to excrete more than the normal quantity of fat in the feces.

Differential Diagnosis

The clinical picture produced by nontropical sprue may be duplicated with more or less exactness by the various diseases that produce secondary sprue syndromes (Table I). In most instances it is possible to make a reasonably certain diagnosis on the basis of clinical, laboratory and roentgenologic findings. Additional help may be obtained by observing the patient over a period of time and noting his response to therapy. There is no doubt that intubation biopsy of the mucosa of the small intestine will become increasingly important as a diagnostic procedure among patients with primary and secondary sprue syndromes. In a few cases, diagnostic exploratory laparotomy may become necessary.

No attempt can be made here to consider in detail each of the various diseases that may produce secondary sprue syndromes. Some of these conditions such as postgastrectomy steatorrhea, gastroileostomy, gastrojejunocolic fistula, and resection or shortcircuiting of the small intestine can be readily suspected from a knowledge of the past medical and surgical history of the patient. Regional enteritis may simulate primary sprue very closely, but can often be distinguished by the fact that many patients with this disease do not have steatorrhea. Patients with regional enteritis are likely to complain of abdominal pain and often have fever, an abdominal mass or external intestinal fistulas. The roentgenologic manifestations of this disease are usually distinctive, but in a few instances may show only evidence of the so-called deficiency pattern similar to that in sprue.

Pancreatic insufficiency, though it produces steatorrhea, rarely simulates the clinical picture of nontropical sprue. This is partly due to the fact that the two diseases that most commonly cause insufficiency of the external pancreatic secretions in adult patients, namely chronic relapsing pancreatitis and carcinoma of the pancreas, are usually associated with severe abdominal pain, which is absent

in sprue. Patients with carcinoma run a relatively short, progressively downhill course in contrast to the long-standing intermittent illness of patients with sprue. Furthermore, even patients with chronic pancreatic insufficiency without jaundice seldom develop nutritional deficiency states of severe degree such as osteomalacia, tetany, macrocytic anemia, hypoprothrombinemia or hypoproteinemia with edema[28]. The D-xylose test may be of help in the few cases in which the differential diagnosis between these two diseases presents a difficult problem, since the urinary excretion of this material following oral administration is usually abnormally low in primary sprue but normal in patients with pancreatic insufficiency[29]. On the other hand, deficiencies in quantity or composition of pancreatic juice obtained by carefully controlled continuous aspiration of the duodenum while the pancreas is being stimulated by secretin (secretin test) may give definite evidence of pancreatic disease and are not usually found in sprue[30,31]. A normal-appearing biopsy specimen of the jejunal mucosa would, of course, favor a diagnosis of pancreatic insufficiency over primary sprue. The demonstration of abnormality of carbohydrate metabolism such as glycosuria, hyperglycemia or a diabetic type of glucose-tolerance curve favors a diagnosis of external pancreatic insufficiency. We have, however, encountered a few cases in which diabetes mellitus was associated with sprue in the absence of other disease of the pancreas[16]. The steatorrheal diarrhea complicating diabetes mellitus with neuropathy may be recognized by the history of long-standing severe diabetes with its complications of visceral and peripheral neuritis, by the demonstration of normal pancreatic function with the secretin test, or by the failure of the steatorrhea to be decreased upon administration of pancreatin[19].

Such rare causes of the sprue syndrome as primary systemic amyloidosis, scleroderma and tuberculosis of the small intestine may be suspected by finding evidence of these diseases in other parts of the body. Primary amyloidosis frequently involves the small intestine and usually can be diagnosed by intubation biopsy of the intestinal mucosa[32]. Lymphomas of the small intestine or its mesentery may cause steatorrhea and in other respects also may simulate the clinical picture of sprue very exactly[33,34]. When no abdominal mass can be palpated and roentgenologic examination reveals no definite evidence of a tumor, surgical exploration may become necessary to settle the diagnosis. Remissions have been reported to occur as the result of treatment for sprue, but these are usually incomplete and last no longer than a few months at the most[34].

Whipple's disease is a rare, chronic, wasting, steatorrheal disorder occurring mostly in middle-aged white men and clinically often resembling nontropical sprue. In addition, there is almost always a history of antecedent migrating polyarthritis and frequently also a palpable abdominal mass, fever, hives, chronic cough, and peripheral neuropathy. A definitive diagnosis can be established only by microscopic examination of the mucosa of the small intestine or the enlarged mesenteric lymph nodes, which reveals characteristic pathologic changes[35].

Results of Treatment

The results of treatment were available in 96 cases in the series[16]. Virtually all of these patients were treated prior to introduction of the gluten-free diet and according to a basic therapeutic program designed to avoid irritating and overburdening the malfunctioning bowel, and to prevent and correct deficiency states. The diet prescribed was restricted in fat and residue but was rich in protein and simple carbohydrates[36]. Vitamins were supplied in the form of multiple-vitamin capsules plus additional Vitamin D, Vitamin K and sometimes vitamins of the B-complex. Supplementary calcium in the form of calcium lactate was frequently prescribed. Iron (if tolerated) and potassium salts were administered orally when indicated. In addition, most of the patients received regular intramuscular injections of liver extract or Vitamin B_{12} or were given folic acid by mouth. This program of treatment we have designated "conventional therapy".

About one-fourth of the patients in the group (mostly those who failed to respond to conventional therapy) were in addition treated with cortisone acetate administered orally. This medication was given in courses of treatment lasting from 1 to several months during which the initial doses, usually of 100 mg. per day, were gradually reduced over a period of weeks or months and finally discontinued as a remission was established[13]. Response of the group treated with cortisone was essentially similar to that of the groups treated by conventional means alone. About one-third of the patients in both groups attained a satisfactory result, since they experienced a good remission with minor or no subsequent exacerbations. Another third of both groups achieved only a fairly satisfactory result, since in spite of the establishment of good remissions they continued to have severe exacerbations of the disease. In the remaining third of each group the results were unsatisfactory, since remissions were either incomplete, did not occur at all, or the patient died of his disease.

The gluten-free diet[37] was employed in only four cases of this series, in three of which it effected a good clinical remission when other therapy had failed. In the fourth case, no benefit was observed from its use. Observation of other patients not included in the series under consideration has demonstrated the value of this diet in the treatment of many patients with nontropical sprue, though not all patients have responded favorably to it. In many cases the clinical improvement in response to this treatment has been most impressive, with subsidence of diarrhea, return of physical energy and recovery of lost weight. Concomitantly, there has been definite change for the better in the hematologic and biochemical picture as well as in the roentgenologic appearance of the small intestine.

Even the patients who responded most favorably to the gluten-free diet, however, have shown persistent evidence of impaired absorption. This is demonstrated by a recent study of 10 patients with nontropical sprue who were

selected for study because they had experienced prolonged and apparently complete clinical remissions of their disease as the result of treatment with a gluten-free diet[38]. In all but one case the diet had been taken for a year or longer and in some instances for 2 years. Six of the 10 patients had experienced symptoms dating back to childhood and no doubt represented examples of celiac disease that persisted into adult life. All patients had experienced a gain of weight ranging from 15 to 60 pounds. They had a sense of well-being, improved strength and ability to work full time. Bowel movements numbered 1 or 2 per day and the stools usually were normal in form and color.

When these patients were subjected to careful tests of small intestinal function, all were found to have abnormalities. Steatorrhea was demonstrated to be present in every case and more than half the patients had flat glucose or Vitamin A tolerance curves. X-ray evidence of disturbed motility of the small intestine was a common finding. Such results are in accord with the findings of others that the microscopic changes in the mucosa of the small intestine are not reversible by treatment with the gluten-free diet or by any other treatment[2,4,39,40]. In our experience, no form of therapy has been found to bring about a complete or permanent return of normal function of the small intestine in sprue. Our findings do not detract from the value of the gluten-free diet in the treatment of nontropical sprue, since in many instances employment of this diet has been clinically successful when all other measures have failed. The results do suggest, however, that: 1. sensitivity to gluten is probably not the sole or underlying cause of sprue though it certainly seems to be an important inciting cause, 2. not all patients with sprue need to be treated with a gluten-free diet, since many of them respond well to a gluten-containing diet restricted in fat and residue and rich in protein and 3. since residual impairment of absorption persists even when good remissions are attained with the gluten-free diet, it seems desirable to supplement this diet (as well as others used in the treatment of sprue) with vitamins and minerals in order to prevent the development of serious deficiencies. Because the gluten-free diet imposes considerable restriction on the patient and entails the use of special recipes for wheat and rye substitutes, we reserve its use for those patients who do not respond well to conventional treatment.

Etiologic Considerations

The cause of primary or idiopathic sprue remains unknown. Among many theories the concept that the disease is produced by nutritional deficiency has probably received the widest support, particularly with regard to tropical sprue. Although severe deficiency states often exist in patients with sprue, it has not been possible to prove that they constitute the underlying cause of the disease, since they may well be secondary to pre-existing impairment of absorption from some other cause. The frequent occurrence of sprue in persons who have always taken a very adequate diet, whether living in temperate regions[16] or in the tropics[41,42], makes it difficult to accept vitamin deficiency as its primary cause.

Furthermore, prolonged ingestion of an inadequate diet prior to the onset of sprue might simply hasten the appearance and accentuate the manifestations of secondary nutritional deficiencies, rather than act as the primary cause of impaired intestinal absorption[43]. This possibility is strongly suggested by the fact that clinical and laboratory evidences of deficiencies quickly disappear with adequate treatment, but evidences of impaired absorption as well as the microscopic lesions in the upper part of the small intestine seem to persist indefinitely[2,16,38-40]. The prevalence of prolonged suboptimal nutrition in the tropics and its relative infrequency in temperate climates might possibly explain some of the differences that have been noted between tropical and nontropical sprue such as the higher incidence of sprue in the tropics, the much more frequent occurrence of megaloblastic anemia in tropical sprue and the more nearly complete and more nearly permanent response of this disease to adequate treatment. Long-standing inadequacies of diet may predispose to the sudden appearance of severe manifestations of deficiency states with the onset of sprue, even though the fundamental impairment of absorption (not caused by the deficiency itself) is mild. In this way, many patients in the tropics may be recognized as having sprue and as being successfully treated for it, whose disease might never have reached a clinical level if they had not been predisposed to the development of deficiency states by previous chronic inadequacies of diet.

In the same way, intestinal infections that occur much more commonly in the tropics than in temperate regions may bring to light mild impairments of intestinal function which in the absence of such an inciting cause would produce no clinical symptoms and would go unrecognized. The fact that some patients with sprue seem to respond favorably to treatment with sulfonamides and antibiotics suggests that infection may play a contributory role[44,45]. The idea that infection is a primary cause of sprue seems to have been largely abandoned because of the failure to identify an infecting organism and of the absence of fever, leucocytosis or anatomicopathologic evidence of inflammation in most cases.

Another etiologic factor of undoubted importance in most cases of celiac disease and in many cases of nontropical sprue is abnormal sensitivity to the glutens of wheat and rye and possibly also to those of oats and barley. As in the case of dietary deficiencies and intestinal infections, most of the evidence available seems to indicate that sensitivity to gluten plays an inciting or contributory role in the pathogenesis of sprue in some cases, but is not the fundamental cause of the disease. Such a viewpoint is strongly supported by the previously cited results of Green and associates[38], who found persistent steatorrhea and other evidences of impaired function of the small intestine in patients with sprue who had made an excellent clinical response over a long period to treatment with a gluten-free diet. It is also strongly supported by the fact that the intestinal lesions of celiac disease and sprue are not reversible by treatment with a gluten-free diet even when the treatment is started early in the course of

the disease[40]. If sensitivity to gluten is a contributing cause in many cases of sprue, the question of possible sensitivity to other dietary constituents must be considered, particularly in patients who do not respond to treatment with the gluten-free diet. It would seem that such possibilities have not as yet been sufficiently explored.

There is considerable evidence to indicate that constitutional and inherited factors are of importance in the etiology of celiac disease and sprue. Rubin and his associates[40] report finding the characteristic microscopic jejunal lesion of celiac disease in each of identical twins, and also in a child with celiac disease and in her mother with adult nontropical sprue. Among other publications that document observations concerning the high familial incidence of these diseases are those of Cooke and associates[12], Davidson and associates[46], Davidson and Fountain[47], and Thompson[48]. On the basis of such data, Adlersberg[15] in 1957 defined primary malabsorption syndrome (in which he included celiac disease, tropical and nontropical sprue) as a "genetically transmitted metabolic disorder", and more recently Weijers and van de Kamer[49] described celiac disease as "'an inborn error of metabolism' which becomes mainly manifest after consumption of wheat (rye, barley, oats)". Among the records of patients with nontropical sprue studied by us, definite evidence of a familial incidence of the disease was very meager[16], but this may well have been due to the fact that no particular attempt had been made to elicit a family history of the disease, and we seldom had the opportunity to examine other members of the patient's family. Our finding that the maximal lifetime weight attained by 63 per cent of the patients in our series, however, was either low normal or below normal and that only 8 per cent ever attained more than normal weight suggests that a constitutional or subclinical absorptive disorder of the small intestine existed long before symptoms of sprue became manifest, possibly dating from the time of birth. In 11 per cent of our patients the symptoms of sprue had their inception in infancy or childhood as celiac disease.

From such evidence it can be postulated that all forms of primary sprue (celiac disease, tropical and nontropical sprue) may be based on some sort of hereditary abnormality of the small intestine, which in many cases is so mild that it may never become clinically evident. Under the influence of certain inciting causes, however, such as dietary deficiency, intestinal infections or sensitivity to glutens, the clinical picture of sprue may be produced in such patients. Patients in whom the fundamental defect is more severe may experience symptoms even in the absence of such inciting causes. The response to treatment in an individual patient would thus depend upon the severity of the underlying hereditary defect and the degree to which the inciting factors are responsible for the total clinical picture. Since these inciting factors can often be removed or controlled by proper treatment, the patient with a mild fundamental defect may be restored to seemingly normal health whereas the patient

with a severe underlying abnormality will continue to have symptoms despite treatment.

Summary

Nontropical sprue is a chronic remittent disease characterized by impaired absorptive and motor functions of the small intestine resulting in multiple and often serious nutritional deficiencies. The disease lacks gross pathologic changes but does display characteristic abnormalities of the mucosa of the upper part of the small intestine, which may be specific. Nontropical sprue must be distinguished from sprue syndromes secondary to other diseases that interfere with function of the small intestine.

There is good evidence to show that nontropical sprue in adult patients is the same as celiac disease in infants and children. Probably also tropical and nontropical sprue are closely related. The term "nontropical sprue" seems preferable to "idiopathic steatorrhea" or "malabsorption syndrome" as a designation for this disease.

A synopsis of clinical findings in 124 cases of nontropical sprue is presented. Many patients with this disease respond very satisfactorily to treatment with a diet restricted in fat, rich in protein and supplemented with extra vitamins and minerals. The gluten-free diet, though not always successful, has been an important contribution to the treatment of nontropical sprue, especially for some patients who do not respond to conventional therapy. The administration of adrenal cortical steroids, usually on a temporary basis, has been helpful in establishing remissions in certain treatment-resistant patients.

Although most patients with sprue respond satisfactorily to some sort of medical therapy, the disease has not been completely or permanently cured by any treatment that we have employed, including the gluten-free diet. For this reason we believe it important to prescribe supplementary vitamins and minerals in all cases.

Although the cause of sprue is not known, there is considerable evidence to suggest that the disease may stem from some hereditary abnormality of the small intestine. The symptoms of sprue may develop as the result of this basic defect alone, or they may be precipitated by one or more additional inciting causes such as dietary deficiencies, intestinal infections or sensitivity to gluten. The response to treatment in any individual patient would thus depend upon the severity of the underlying hereditary defect and the degree to which the correctible inciting factors are responsible for the total clinical picture.

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Discussion

Dr. Samuel L. Governale (Chicago, Ill.):—It would be preposterous for me, as a surgeon, to discuss the essayist's excellent contribution. I, therefore, take advantage in the perusal of the literature that there are about 38 contributory causes to the advent of idiopathic nontropical sprue.

I must lean heavily upon the facets of the surgical implications. It is my observation from the perusal of the literature that 19 of the 36 causes are either the result of or the lack of surgical therapy rendered to such patients.

To mention only a few and as alluded to by the essayist, I will only refer to the 1. subtotal and total gastrectomies, which result in malabsorption, 2. bowel resection, 3. the Zollinger-Ellison syndrome, when it's unabated in its extensive clinical havoc to the host, and the lack of treatment in the diverticuli of the small bowel, stomach, strictures, adhesions and blind loops, etc.

Now I can hurry this thing along if I may now have the first slide.

(Slide) This is a patient whose age is 42 and on 1 July 1936 she underwent a colectomy concomitant with a panhystero bilateral salpingo-oophorectomy for advanced endometriosis of the pelvic organs.

The reason that the colectomy was done simultaneously was a lesion. . . .

(Slide) which at operation disclosed an abnormal contracted area at the rectosigmoid level.

Because of the ambiguity of the lesion the two operations were done concomitantly.

This patient, since the operation, has suffered a great deal of malabsorption, averaging from 10 to 15 bowel movements or diarrhea without the fatty undigested elements therein.

(Slide) The next case is that of a female, 39 years of age and you are now looking at a picture which is an hour after the gastrointestinal series was begun. The case was erroneously diagnosed as a terminal or regional ileitis.

This 63-year old lady had a lesion as you can see at the terminal ileum and it was diagnosed as a Crohn's disease; had had many attacks of diarrhea prior to admission into the hospital with abdominal pains; an ileohemicolectomy was carried out and right ileotransversostomy.

This patient has been ameliorated considerably and thus far, since 1957 she has had an uneventful recovery with no diarrhea. This case depicts a clinical improvement by surgery.

(Slide) This is a man, 55 years old, who had a high benign gastric lesion, as you can see, in this area, and had another in the duodenum.

The lesion was interpreted by the roentgenologist as being a suspect carcinoma and the reason I'm showing you this slide is that we did a 95 per cent

gastrectomy following which the patient developed symptoms of malabsorption, anemia, etc., and diarrhea.

(Slide) This shows the remnant portion of the stomach and he has not had any postoperative gastrojejunal ulceration.

(Slide) This man had been operated several weeks prior to 16 January 1948 at which time he developed adhesions of the abdominal wound with massive mesenteric occlusion. I want to mention this case because he had three-quarters of the jejunum and three-quarters of the terminal ileum resected. Postoperatively he developed considerable diarrhea, 10 to 20 bowel movements daily and lived approximately about four years and four months postoperatively.

In conclusion, I wish to thank the essayist for the privilege of discussing his timely paper.

Dr. E. E. Wollaeger (Rochester, Minn.):—I would like to thank Dr. Governale for his remarks. I agree with the emphasis he has placed upon the fact that diseases other than primary sprue, which interfere with the function of the small intestine, may cause secondary sprue syndromes difficult to distinguish from the primary variety. All patients presenting the clinical picture of sprue should be carefully examined for such disease.

Intubation biopsy of the upper small intestinal mucosa has been demonstrated to have definite diagnostic value in most cases of idiopathic nontropical sprue in which pathologic changes are relatively marked. The significance of lesser degrees of similar pathologic abnormality is not now clearly evident, and in our opinion it is not yet possible to establish or to eliminate the diagnosis of nontropical sprue in such cases solely on the basis of biopsy evidence. A diagnosis of diseases causing secondary sprue syndromes such as systemic amyloidosis and Whipple's disease can often be established with certainty by means of the biopsy technic.

I have a question submitted from the audience, "Have you any opinion as to the role of steroids in the therapy of sprue?" Time did not permit discussion of steroid therapy in the course of my talk. I believe adrenocortical steroids have a place in treatment of nontropical sprue particularly in patients who do not respond well to other forms of treatment, i.e., to conventional therapy as I have outlined it or to the gluten-free diet. In many such patients, some of whom were very seriously ill, we have found that cortisone has helped greatly in the establishment of satisfactory remissions.

We do not like to use steroids on a long-term high-dosage basis. Customarily we start with 100 mg. of cortisone acetate in four 25 mg. doses per day by the oral route. After one to three weeks at this level we gradually cut down the dosage in a steplike manner as a remission takes place, aiming to eliminate the cortisone completely over a period of several weeks. In only a few patients has it been found necessary to continue to administer small amounts of cortisone (not exceeding 25 mg. per day) for an indefinite period of time.

COMMON ERRORS IN NUTRITION*

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Philadelphia, Pa.

Since I am certain that the data which I am presenting is common knowledge, I think we might retitle this presentation "Oversights in Nutrition".

For purposes of discussion, errors in nutrition may be divided into errors of commission and errors of omission. Among those committed in the prescription of therapeutic diets is the use of regimens which are impractical. Sometimes the patient can't obtain the food, won't accept the radical change, or the diet fails to consider such items as idiosyncrasies, religious dietary restrictions or racial food habits or characteristics.

Another instance is in patients in whom weight gain is desired either due to undernutrition *per se* or after periods of profound stress such as chronic illness or surgery where increased caloric intake is desirable. The prescription of a diet high in calories, and high in proteins and/or fats or carbohydrates to a patient who has up to that point been taking only small amounts of food, is a failure to face reality or understand the problem at hand. A patient who has been eating 1,200 or less calories a day can hardly be expected to begin to take in 3,000 or more calories a day simply by the prescription of such a diet. These people are not used to such a volume of food and are unable to eat it without physical distress as well as mental anguish. The sudden increase in the diet prescription in this manner frequently leads to a feeling of hopelessness on the part of the patient and an abandonment of any attempt to actually increase the dietary intake. It would be preferable to increase the caloric consumption by small increments over a period of time up to the caloric level desired. Such a program is more easily accomplished by the patient, and at each level of increase the likelihood of achieving the extra consumption is more realistic. The accomplishment of the increase gives the patient not only a sense of well-being but an added sense of accomplishment and therefore the interest and desire to proceed. Another error, not infrequently committed by physicians is the condoning of abnormal or fad diets. An example of this is a purely liquid formula diet for weight reduction. In this case, it is sometimes quite possible for the patients to lose weight on such a diet and for the formula to be nutritionally adequate. I feel, however, the error in this type of diet lies in the use of an unrealistic or unusual dietary regimen. It is not only the desire of the attending physician to achieve a therapeutic result, but also in the course thereof to train his or her

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patient in proper eating habits so that at the end of the period of therapy there will be a continuation of good eating habits and a maintenance of the status of health thereby attained. It is unlikely that a patient who, loses weight on a liquid diet will then, having achieved the level of weight loss desired, suddenly and miraculously begin to eat a normal, wholesome, well-balanced diet and maintain the weight loss. Consequently, the use of such a diet defeats the most important aim of nutritional therapy. Furthermore, this failure may have additional deleterious effects in that it causes the patient to experience repeated episodes of weight loss and gain with the accompanying repeated lipemias and the potential dangers that this might represent. Another practice that one sees not infrequently is limitation of water intake and/or the restriction of salt intake in patients on reduction diets who are otherwise healthy. Such practices are certainly not sound and only tend to make the patient more uncomfortable in an already difficult dietary situation.

Another nutrtional practice which may raise a philosophical question rather than be classified as a true error is the use of a diet regimen which markedly alters the normal or usual pattern of the diet. The use of fat-free diets, or diets high in unsaturated fats in the treatment of hypertension and/or arteriosclerotic heart disease, although supported by much currently available data which suggests that these practices may have some value, nevertheless, raises a question as to what the possible long range effects that such major changes in diet may have upon the body's metabolic economy. The information supporting such major changes in the diet are still not completely confirmed, nor the beneficial effects completely substantiated. The general use of such dietary alterations in the absence of definitive data concerning both the value and possible ill effects of such a program must continue to be questioned.

Probably more common than errors of commission are the errors of omission in the treatment of patients requiring dietary support. One such important area where therapeutic nutrition is overlooked is in the postoperative patient. Often these patients are maintained on liquid intake for long periods which are totally inadequate in caloric content, or in protein which is so badly needed during the period of tissue repair and metabolic stress. In the postoperative or comatose patient who requires intravenous nutrition, supplemental vitamins are frequently overlooked in the infusion. There is also a tendency to neglect the use of the newer modalites available to help supplement the nutrition of this type of patient. Although they must be used with care, the intravenous fat emulsions, protein hydrolysates and alcohol are valuable adjuncts to the armamentarium of the nutritionist. In the patient who is able to take an oral diet, there is frequently a marked discrepancy between the prescription and the diet consumed. The error here is frequently the physician's inability to take the necessary time to instruct his patient in the diet. When he cannot himself take the time to review the details of his dietary prescription, then he should utilize the talents of the hospital dietician or the public health nutritionist. It is extremely important that

therapeutic nutrition not only be prescribed but that the patient understands it sufficiently so as to be able to execute it effectively. Another oversight one frequently finds is the failure to supplement therapeutic diets which have restrictions such as hypocaloric diets, low-fat diets, etc. with adequate vitamins and minerals to make up for those which are not supplied by the regimen ordered. There is also an under use of vitamin and mineral supplementation in patients or long-term chemotherapy, particularly the antibiotic agents where absorption is interfered with by the use of the drug. In this case, supplementation becomes an extremely important adjunct to treatment. When using vitamins therapeutically, better results will be achieved by giving them in divided doses rather than as single massive doses. It has been shown that absorption is much more effective when the total dose is divided.

In conclusion, I might then summarize by stating that the greatest error made in nutrition in medicine today is the failure to make the best use of it in the active treatment of disease.

Discussion

Dr. Seymour Lionel Halpern (New York, N. Y.):—Dr. Tauber's concluding observation is one which cannot be sufficiently stressed.

The principal, most grievous and unpardonable error currently encountered in nutrition is the failure to properly utilize the nutrition knowledge which has evolved during the past several decades.

There is available at present, sufficient data on the requirements for various nutrients in health and disease, on the composition of various food substances, on methods of food preparation, and on the dietary habits of the various ethnic groups in our cosmopolitan nation, to enable every physician at all times to ensure an adequate nutrient intake by all patients. This applies to every commonly encountered physiological and pathological state.

Considering its importance, nutrition education in the public schools, colleges and among the laity in general, has been remarkably inadequate. Unfortunately, this is also true of Medical Schools, postgraduate interne and resident training programs, and among practicing physicians.

Diet is an intrinsic part of all therapy, and physicians should be sufficiently versed to enable them to properly answer their patient's questions with clarity and without relying too strongly on preprinted diet schedules.

The physician should know what foods can be eaten as well as what cannot. He must be familiar with the nutrient values of all common foodstuffs. He, himself, must know how to compose a therapeutic diet. He must know precisely the limitations, as well as the indications, for the various food regimens he prescribes. An inadequate knowledge of the science of nutrition, because of an

over-concentration during training on esoteric and rarely met diseases, can result in an otherwise excellent therapeutic program going bankrupt.

In the few minutes alloted to me, it is not feasible to attempt even a brief review of the basic fundamentals of nutrition. The medical library can fill this need.

I would rather utilize my time to underscore certain remarks made by Dr. Tauber while taking exception to others.

I am in accord with Dr. Tauber's comments relevant to the physician's being sure that a proposed diet is ingested. It is not sufficient to compose and prescribe a sound and nutritious diet; attention must be paid to many salient auxiliary features such as appetite, cultural factors, dietary habits and idiosyncrasies, the state of dentures, facilities for preparing food and other environmental factors.

You are all aware that the principal nutritional disturbance in the United States today is caloric overnutrition and obesity, resulting from the over-abundance of foodstuffs and our eating habits. The recent Build and Blood Pressure Study of the Society of Actuaries has reemphasized the dangers of obesity and its catacylsmic effects on many of the body's biochemical and physiological mechanisms. There can be no doubt that significant overweight is associated with both increased morbidity and mortality.

It is a serious error not to institute at an early age, measures which will prevent the development of overweight. Education should begin in the school years. The majority of people who become fat as they grow older, do so, not because of gluttony, but because caloric intake remains stationary, while caloric needs decrease. People are less active as they grow older, automation in industry and spectator activities in leisure decrease caloric expenditure, energy needs lessen when active body growth is terminated and the tissue metabolic rate diminishes with age. By tailoring the total diet calories to meet the body's decreasing needs as one grows older, so-called "middle age spread", with its harmful consequences, can be circumvented.

Dr. Tauber is correct in decrying unusual dietary regimens and fad diets. In the case of obesity, however, we cannot discount the excellent results which are being achieved by the use of a liquid formula diet. Numerous individuals who have failed to overcome obesity through the use of standard diets, have reduced successfully by using a prepared formula diet containing 900 calories. Attempts to restrict natural food intake to 900 calories frequently leads to a dietary inadequacy and the diet is seldom adhered to by the patient. Upon abandoning such a diet there is usually a rebound effect and lost weight is rapidly regained.

Contrariwise, there are no failures when a patient adheres to a 900 calorie liquid formula diet, no subclinical malnutrition is introduced and the patient

usually cooperates with the regime knowing that it is only a temporary expedient. I find that the patient is encouraged by the weight loss and by the improved personal appearance, health and feeling of well-being which he achieves in a brief time. When such patients are returned to a regime containing food, they are usually anxious to sustain and continue their favorable progress. In addition, it is less onerous for them to follow a low calorie diet, since there appears to be a surfeit of solid foods after completing the liquid formula diet program. It has been my personal experience that patients who have reached their normal weight through the fixed formula preparation, have been more successful in maintaining the desired weight than patients who reduced by a low calorie solid food diet.

There is no substitute for the proper indoctrination of good eating habits, and this should be taught to the patient no matter which type of diet he is following.

In closing, I want to thank Dr. Tauber for this opportunity of discussing his paper and hope that many of you in the audience will join us in the crusade to improve health and longevity by utilizing the ever expanding knowledge of nutrition.

Dr. Sanley A. Tauber (Philadelphia, Pa.):—I'll just make this one very short comment on our point of difference, Dr. Halpern. I think the point that I would like to get across concerning the use of liquid formulations, for instance, for weight reduction is that I feel the basic problem is not the weight loss.

I like to emphasize to my patients that weight loss is merely coincidental to the problem of diet re-education. I still can't believe that a patient who has lost weight on a liquid formula diet, who had poor eating habits to begin with, and then goes back to a whole diet once again, can be miraculously transformed or re-educated in their eating habits or their dietary habits. They need conditioning and this they can only do as far as I can see it by repetitively eating three intelligent meals a day during the process of weight loss so that by the time they have lost their weight they are beginning to develop eating habits which will stay with them and which will help them.

I like to emphasize to my patients that the most important six months of their diet is not during the weight reduction, but the six months subsequent to their having achieved their normal weight range. As I say, I appreciate that you tell us that you've had success with the liquid formulas; on the other hand I would like to see your one-, two- or three-year follow-ups to see if they retain their weight reduction using liquid formulas as a primary program for reduction.

THE USE OF RADIOACTIVE-LABELED LIPIDS IN THE STUDY OF FAT ABSORPTION IN VARIOUS DISEASES OF THE GASTROINTESTINAL TRACT*

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Philadelphia, Pa.

The measurement of fat absorption up until the present has been difficult to undertake. Balance studies involve many problems on the part of the patient, the nursing staff, and the laboratory and are generally not in great favor. Duodenal intubation procedures to determine pancreatic function are even more difficult and are performed in only a few institutions.

The recent availability of radioactive-tagged lipids now makes it possible to study such problems in a much simpler manner than was heretofore possible. The present report summarizes our experiences with the use of these materials in various diseases of the gastrointestinal tract.

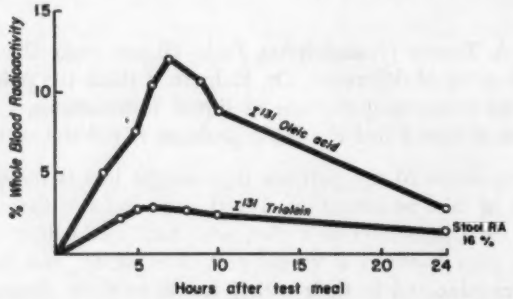

Fig. 1—Radioactive lipid absorption patterns in steatorrhea due to pancreatitis.

TECHNIC

An oral fat meal containing 25 microcuries of I^{131}-triolein in a diluent of peanut oil to make a final volume of 1 ml. of fat/kg. of body weight is administered after an overnight fast. Venous blood samples are taken at frequent intervals thereafter until a peak blood radioactivity concentration is reached (usually by the 6th hour) and then again after 24 hours. Stools are collected over a 48-72 hour period and are also assayed for radioactivity.

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Misleading results may be obtained if a smaller amount of fat, i.e., a capsule fat meal is ingested as has been suggested[1] or if the blood sampling is discontinued before a maximum blood radioactivity concentration has been reached.

Differential diagnosis of steatorrhea:—Although many etiological causes for steatorrhea are known there are two basic mechanisms involved in its causation—a defect in digestion whereby neutral fats are hydrolyzed incompletely or not

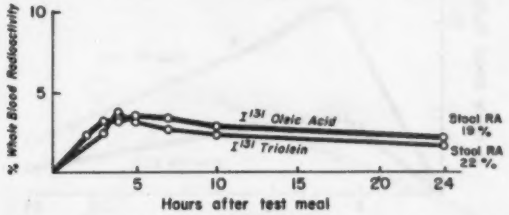

Fig. 2—Radioactive lipid absorption patterns in steatorrhea due to sprue.

at all due to a deficiency of pancreatic lipase and thus cannot be absorbed, and the other—a defect in the absorption surface of the intestinal lumen, digestion in this instance being normal. Prior to the advent of isotopes, the differential diagnosis of these two conditions was virtually impossible.

Figure 1 shows the typical radioactive fat absorption pattern obtained with I^{131}-triolein and oleic acid in a patient with steatorrhea due to chronic pancrea-

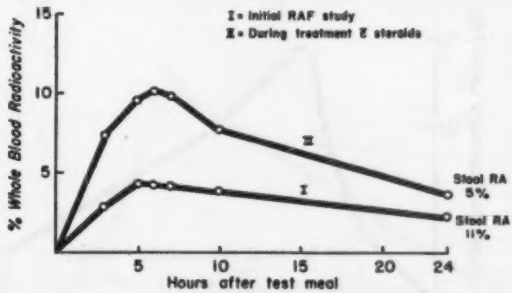

Fig. 3—Improvement of fat absorption in sprue with steroid therapy.

titis. The deficiency of lipase is manifested by a flat triolein curve with an elevated fecal radioactivity. Absorption of oleic acid (which is already hydrolyzed) is normal.

Steatorrhea due to sprue is characterized by different absorption patterns. In this condition both triolein and oleic acid are poorly absorbed (Fig. 2).

Evaluation of degree of improvement in fat absorption in malabsorption syndromes:—Isotopic fat studies may also be used to good advantage in the

management of patients with various malabsorption diseases to evaluate the degree of improvement during a course of treatment. Figure 3 shows the fat absorption curves in a 32-year old male with sprue before and during therapy

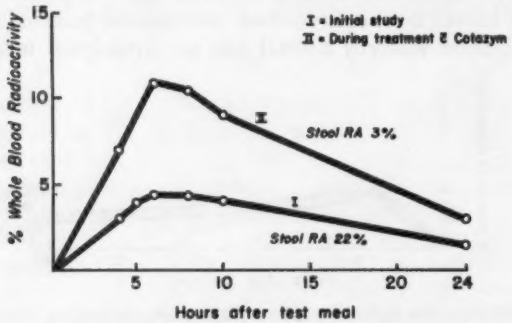

Fig. 4—Improvement of fat absorption in pancreatitis with Cotazym therapy.

with steroids. The marked improvement in fat absorption correlated well with his clincial response.

Figure 4 demonstrates the increased absorption that resulted in a patient with chronic pancreatitis who was being treated with Cotazym, a new and

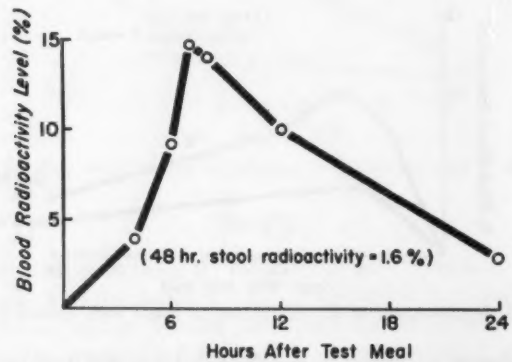

Fig. 5—Radioactive fat absorption in jaundice due to infectious hepatitis.

potent pancreatic extract. The maximum blood radioactivity level (11 per cent) was in the normal range with a stool content of 3 per cent as opposed to the pretreatment value of 22 per cent. Hightower[2] and others[3] have also reported favorable results with this preparation in children with cystic fibrosis and other malabsorption states.

We have also been able to show the existence of impaired fat absorption in various other conditions such as congestive failure[4] and functional diarrhea[5] and to demonstrate the improvement which resulted when compensation was regained in the first instance or when the intestinal hypermotility was normalized with antimotility agents in the latter state.

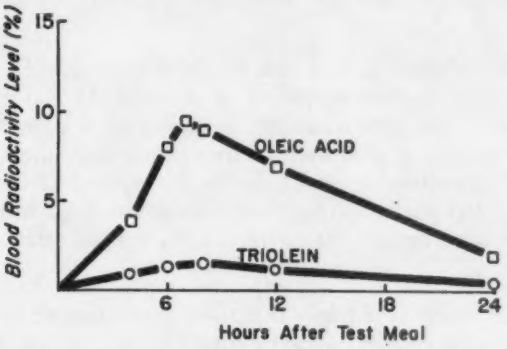

Fig. 6—Radioactive lipid absorption patterns in jaundice due to carcinoma of the pancreas.

Differential diagnosis of jaundice:—Another area where I^{131}-neutral fat or fatty acid technics are of value is in the differential diagnosis of jaundice. The basic principle which influences the over all configuration of these absorption patterns may be applied to good advantage in the icteric patient. Thus, if ade-

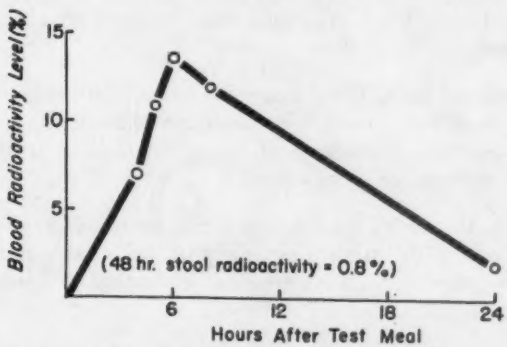

Fig. 7—Radioactive fat absorption in jaundice due to chlorpromazine.

quate amounts of pancreatic enzymes and bile salts are able to enter the small intestine, normal neutral fat absorption will occur. If, however, an obstructive process is present which prevents partially or completely the entrance of these products this will be reflected by an abnormal blood radioactivity absorption curve with a corresponding increase in the fecal isotope excretion. Thus, in

infectious hepatitis, normal fat absorption may be anticipated and does occur (Fig. 5). On the other hand, extrahepatic obstructive jaundice due to carcinoma of the pancreas is usually associated with a flat triolein curve. Oleic acid absorption is normal, however, in most cases (Fig. 6). We have found that a maximum blood radioactivity level of less than 4 per cent with an elevated stool activity in a jaundiced patient is fairly conclusive evidence for carcinoma of the pancreas[6].

It has been in cases of jaundice resulting from intrahepatic cholestasis, however, that these procedures are of most value. In this condition, which recently has been seen with increasing frequency as a complication of newer drug therapy especially in the psychopharmacologic field, the clinical and laboratory differentiation from surgical jaundice is frequently difficult. The ability, however, of bile and pancreatic enzymes to enter the duodenum in this process as opposed to extrahepatic cholestasis allows for adequate radioactive fat absorption (Fig. 7).

It is not our intention to imply that these newer tagged fat procedures can replace the older chemical fat balance studies. On the contrary, we[7] and others[8,9] have found them inadequate and misleading in many instances. Nonetheless, if they are carefully done according to a precise methodology and their results interpreted accurately, they will furnish the clinician with a vast amount of information which he may otherwise be unable to obtain.

Summary

Radioactive-tagged lipids are useful tools to study fat absorption in gastrointestinal diseases.

After an oral test meal, blood and stool analyses are helpful in determining whether malabsorption is present, whether it is due to an absorptive or digestive defect, and in assessing the degree of improvement after treatment with pancreatic extracts, steroids, or other agents.

Furthermore, the use of these technics may be of differential diagnostic importance in patients with jaundice especially of the intrahepatic type where the clinical and laboratory findings are frequently identical to those found in extrahepatic surgical jaundice.

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Discussion

Dr. Benjamin O. Morrison (New Orleans, La.):—I found this a very interesting paper from the standpoint of the fact that there are three or four things of particular interest.

It might be that Dr. Berkowitz could elucidate further on these problems.

One is the not often associated iron deficiency anemia with sprue which, we could see from his tests, the loss of iron could probably be in conjunction with the loss of fat.

I had one such case of diverticulitis with the typical sprue syndrome that had an iron deficiency anemia and whenever the patient had an attack of diverticulitis he developed a marked malabsorption syndrome, iron deficiency anemia, foamy stools and I see now with the use of this very excellent diagnostic agent that we have something that we can use to explain why these cases do as they do.

The next point I want to bring up was the use of Cotazym as a replacement for crude pancreatic extracts in cases of pancreatitis.

I feel sometimes that this is an apparent improvement on the old pancreatin which we had before, which actually was a combination of all three enzymes, this being—we're not putting in a plug for one of the laboratories, but we feel that this is an improvement on the old pancreatin.

The third thing I wanted to mention was the fact I'm very glad to see somebody else substantiate the theory that imperfect fat absorption can not only be produced in phthisis but also coronary atherosclerosis.

Not only do we have the basis—we have the association here, but we have a test which will substantiate this fact.

I can't think of any other thing except the very interesting differential diagnosis between intrahepatic and extrahepatic jaundice.

I need not elucidate upon that further because I'm sure that Dr. Berkowitz knows a whole lot more about that than I do.

THE MANAGEMENT OF PATIENTS FOLLOWING EXTENSIVE INTESTINAL RESECTION*

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New York, N. Y.

Massive resections of the small intestine are most frequently performed for extensive involvement by nonspecific granulomatous enteritis and for mesenteric arterial or venous thrombosis. Less frequent indications are gangrene due to volvulus, intussusception or herniation accompanied by interference with blood supply, neoplasm, necrosis of small bowel due to prolonged intubation with the Miller-Abbott tube and external trauma.

The average length of the small intestine as determined by measurements at operation or autopsy in 1,161 cases by Haymond[1], was 21 feet 6 inches or approximately 650 cm. A massive resection may be considered to be one in which at least one-third, or seven feet, of the small intestine has been excised. Haymond[1] in 1935, reviewed 257 cases of massive resection with a total mortality of 33.5 per cent. He thought that a patient could return to normal with 35 per cent resection and that a 50 per cent resection was the upper limit of safety; but since 1935, there have been many case reports indicating that half the small intestine can be removed without resultant symptoms, and that two-thirds (or 14 feet) of small intestine can be resected without serious risk. Holman[2] reported a case in which 20 feet or 609 cm. of small intestine were resected with recovery. Althausen[3] reported a case in which 90 per cent of the small intestine was resected with recovery, the patient reaching a nutritional equilibrium after ten months, although only 45 cm. of small bowel remained. More recently, Berman[4] et al have reported the survival of a patient in whom all but 18 inches or 45 cm. of small intestine were resected.

The management of patients with extensive small bowel resections, who have survived surgery, is essentially a nutritional problem. As Kiefer[5] has pointed out, this problem is a much more difficult one in those patients whose indication for resection has been diffuse jejunoileitis. Involvement of the remaining small intestine by inflammatory process, and the great tendency to recurrences, as much as 34 per cent in some series, render the maintenance of adequate nutrition in these patients a much more difficult problem than in those patients where the indication for resection is a noninflammatory disease. A sprue-like syndrome, marked by weight loss, diarrhea and steatorrhea, flatulence, hypoproteinemia, peripheral edema, anemia, hemorrhagic tendencies and hypocalcemia, which may or may not result in tetany, is often encountered in patients where extensive

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resection is done for jejunoileitis. On the other hand, more extensive resections of small intestine have been performed for mesenteric thrombosis without causing permanent impairment of nutrition.

The nutritional problem in patients with extensive resections of the small intestine for inflammatory disease is usually so difficult that it would seem advisable not to perform such resections unless a case of jejunoileitis is attended with obstruction or by fistula or abscess formation. In some patients with extensive uncomplicated jejunoileitis, the results of conservative medical therapy are surprisingly good. A low-residue diet, blood transfusion, parenteral crude liver extract and vitamin supplements, and small doses of steroids may produce a clinical situation far more satisfactory than that which would be obtained after an extensive resection of the disease process.

A patient who has had a massive intestinal resection makes certain adjustments. The lumen of the residual small bowel increases in size and its wall becomes thicker. On x-ray, a coarsening of the mucosal pattern is present. Lundquist[6] cites Monari who showed in dogs that the mucous membrane doubles its normal thickness and the villi become larger and more numerous after massive resections. Flint[7] stated that there was a 400 per cent increase in the absorptive area of the small bowel as a result of this marked hypertrophy of the mucosa. The initial weight loss leads to a lower basal metabolic rate and a lessened caloric requirement, so that finally the nutritional needs may be balanced by the increased absorption, and weight may be stabilized.

Pullan[8] has summarized very well the stages of recovery in those patients who survive a massive resection. First: the postoperative fluid and electrolyte crisis, with severe diarrhea, which may last two or three weeks; the phase of recovery and adaptation, which may last from one to two years; and finally a stage in which, if recovery is incomplete, the patient learns to live with his disability.

Return of intestinal motility in the immediate postoperative period results in a profuse diarrhea associated with tensmus, burning and perianal irritation. Fluid electrolyte losses may be enormous. All fluid losses must be charted and replaced intravenously with careful electrolyte replacement. Intravenous fat solutions and protein hydrolysates may be helpful when this stage is prolonged. A urinary output of 1,000-1,500 c.c. should be maintained.

As the diarrhea decreases, attention shifts from fluid and electrolyte balance to nutrition. There is a rapid loss of weight despite large food intake, much of which is lost in the stools. Normal oral feeding is resumed as soon as possible. Food intake should be frequent and in the most massive resections almost continuous, so that the remaining small bowel mucosa is used to maximum advantage.

The greatest difficulty after massive small bowel resections involves the utilization of fat. Todd's[9] patient with 90 cm. of small intestine excreted 45 per cent of ingested fat in the feces. The ability to hydrolyze fats is not impaired, but absorption is impaired. The excreted fat is largely in the form of fatty acids. If there is little fat excreted in the form of soaps, calcium deficiency may not result. When insoluble calcium soaps are excreted, hypocalcemia and tetany may result. It is probable, however, that loss of Vitamin D may be a greater factor in producing hypocalcemia than loss of calcium in excreted soaps. With the passage of time, there may occur an adaptation of the remaining small intestine, so that a larger proportion of ingested fats is absorbed. Fat in the diet should be restricted to tolerance. In general, a low-fat diet is required, but dairy fats in cream and butter may be given to tolerance. The use of synthetic types of predigested foods, of papain (which is often effective in reducing fecal fat in pancreatic insufficiency) and of "Tween 80" has not led to any improvement in absorption of fat in these cases. Where hypocalcemia is present, which is unlikely if more than six feet of bowel remain, large doses of calcium should be given orally, and Vitamins A and D should be given in doses of 100,000 to 200,000 units daily.

There is experimental evidence which indicates that the distal portion of the small intestine plays a more important role in the absorption of fat and maintenance of weight than the proximal portion. The preservation of the ileocecal valve and the entire colon has been shown to decrease fat, nitrogen and electrolyte excretion in the stool, so that wherever it is possible, in performing a massive resection, the ileocecal valve should be retained to maintain its function of delaying the entrance of nutrients into the colon and in order to allow increased time for absorption in the ileum.

Protein absorption is relatively good and a positive nitrogen balance can usually be maintained. Althausen's[8] patient with only 45 cm. of small bowel left, utilized 62 per cent of ingested protein, and Todd's[9] patient with only 90 cm. of small intestine, retained 76 per cent of ingested protein. Normal serum proteins may be found in some cases. It appears that a small amount of jejunum is necessary for the absorption of proteins. The colon may absorb large amounts of amino acids, as shown by experiments in which amigen was injected into the colon. The diet should be low in fat, high in carbohydrate and high or medium in protein. Roughage is avoided.

In most cases of massive resection of the small intestine, carbohydrate absorption and utilization is approximately 100 per cent efficient. Nevertheless, symptoms of carbohydrate indigestion, such as abdominal distention and flatulence, occur. This is due to hypermotility, which causes the passage of starch which has not been completely hydrolyzed by enzymes into the colon. Fermentative bacteria in the colon act on the unabsorbed carbohydrate with the production of gas and organic acids, resulting in distention and flatulence. It is recommended that carbohydrates be supplied in the form of glucose rather than

starches. Althausen[3] reported that his patient was relieved of distention and flatulence when glucose was the only source of dietary carbohydrates.

To control intestinal hypermotility, one should avoid irritating foods, foods that are too hot or cold, and too much liquid with meals. Antispasmodics, bismuth and opium and sedatives may be of value. Inactivity after meals may be helpful.

To sum up, in the management of massive small intestinal resection: surgically, the postoperative difficulties may be greatly reduced by retaining the ileocecal valve and the colon wherever possible; medically, a moderate high protein, low-fat diet with liberal allowance of carbohydrates chiefly as glucose rather than starch is indicated. Feedings of cooked food should be frequent and of natural foods preferably. Food should be appetizing and varied. Serving of food in the pureed state is generally not necessary or advisable, since it tends to decrease appetite. Supplementary Vitamins A, B, C and D are administered by the parenteral route. Vitamin K may be necessary if there is any bleeding tendency. Transfusions of blood for anemia are employed, but anemia is rare if the remaining small bowel is normal and there is no chronic bleeding. If hypoalbuminemia and edema are present, salt-free albumin is given intravenously, and the protein intake is made as high as tolerated. Oral and intravenous calcium are administered when necessary, and other electrolyte disturbances are appropriately treated. Small doses of cortisone and ACTH may have a very favorable effect on intestinal function and in decreasing diarrhea.

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Discussion

Dr. Irving Sokolic (Philadelphia, Pa.):—I should like to thank you and Dr. Weingarten for the invitation to discuss this paper.

As a surgeon I am myself more concerned with the immediate management of patients with extensive small bowel resections and in my own personal experi-

ence the vast majority of these cases are due to vascular disease either venous or arterial.

The approach as far as the surgeons are concerned is becoming more and more conservative. We're attempting to preserve as much bowel as possible and insofar as doubtfully viable bowel is concerned our present feeling is to leave the doubtful bowel *in situ* and instead of doing a primary anastomosis, bring out the obviously viable proximal small bowel as a sidetracking jejunostomy to reconstruct the gastrointestinal tract at a later date when the viability of distal bowel is more apparent.

Another point that we as surgeons are concerned about and Dr. Weingarten emphasized is that if at all possible every attempt should be made to conserve the ileocecal valve.

Unless this area is frankly gangrenous my own feeling is to leave the valve intact and come back and re-examine it at a later date, usually the second, third, fourth day after the emergency operative procedure.

In this fashion we hope to achieve some semblance of long-term survival. In my own experience, long-term survival after massive bowel resection is relatively small. Of 17 patients resected, only 3 are alive at the end of five years. The vast majority of those who do survive the immediate postoperative period will inevitably die in nutritional imbalance, most likely a nutritional type of cirrhosis.

The surgeons are concerned about these problems and some of the newer approaches being advocated might be apropros of this particular meeting.

One of the more recent concepts is that advocated primarily by Cohn in Louisiana. During operation he will insert antibiotics locally into vascularly compromised lumen of the small bowel. With local antibiotic protection he has been able to demonstrate that segments of dog bowel, at least 20 cm. long, have been able to be protected from the effects of the ischemia and the resultant bacterial invasion merely by local installation of neomycin. This approach, coupled with the sidetracking procedure makes sense.

Some of the other problems that we as surgeons are considering is reconstruction of new ileocecal valve. It has been possible, at least in dogs, to provide a partial blockade of small bowel passage by taking a small segment of small bowel and reversing it so that the peristalsis in the reversed segment of small bowel now runs in an antiperistaltic fashion. If one uses a segment as small as one inch one can delay the emptying from the proximal small bowel by as much as 50 per cent.

I'm a little bit concerned about trying it in humans; one is concerned about the problem of subjective pain, etc., associated with partial small bowel obstruction.

The long-term program outlined by Dr. Weingarten is excellent; I have no additions to make; I feel that one should be optimistic in this particular disease. To that end there is a case report in the *South African Medical Journal* of at least nine-year survival of a man who had only seven inches of proximal jejunum left and only half the large bowel.

Dr. Michael Weingarten (New York, N. Y.):—I'm sorry that Dr. Berkowitz is not here to answer the question, but I suppose the question might have been directed to me as well and therefore I'll try to answer it if I can.

"I'm not sure that the radioactive triolein study shows the full extent of failure to absorb fat. In many patients with malabsorption, there is an overlapping of normal and abnormal values with this method. Was the fat in the stools quantitatively determined?"

In this particular patient there was normal radioactive capacity, but with the sprue-like clinical syndrome there was loss of weight for a matter of three or four years.

"Were there cases of regional enteritis who had massive resections?"

No. They were both cases of gangrene of the bowel with postoperative lesions. There was diarrhea immediately after intake of food.

It's very difficult for me to conceive that such a patient would have a normal fat absorption. If there was so much hypermotility that every time the patient ate, he had a bowel movement, I find it very difficult to explain how the radioactive study of fat absorption would show a normal result. Perhaps there was some technical error in the performance of the test.

Of course, protein absorption is never 100 per cent in these cases. You may get 60 to 70 per cent absorption but it's not 100 per cent and these patients lose a great deal of weight, but finally their weight becomes stabilized at a given level.

TWENTY-FIVE YEARS' EXPERIENCE WITH PANCREATITIS*

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and

H. T. BLUMENTHAL, M.D.

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Twenty-five or 30 years ago the diagnosis and treatment of diseases of the pancreas was very indefinite and uncertain. In the 30's two men, the late Robert Elman of the Washington University School of Medicine, and Alan Whipple, became interested in two subjects which were extremely hazy at that time: acute pancreatitis by Dr. Elman and carcinoma of the pancreas by Dr. Whipple. Dr. Elman felt that if we could establish some sort of a laboratory test which might give us a clue that the pancreas was involved it might make a great difference in the subsequent diagnosis, treatment and life of the patient. At that time Dr. Michael Somogyi, who was our biochemist at the Jewish Hospital of St. Louis, was prevailed upon to develop a test which might give us a clue as to when the pancreas was involved in an acute inflammation.

In 1932 or 1933 Dr. Somogyi did develop and give to us what is now known as the Somogyi diastase or amylase test. In order to get some idea as to where and what the test would mean, every patient admitted to the Jewish Hospital that year had blood drawn and a diastase test performed. Not only was this done at the Jewish Hospital, but, to a great extent, at the City Hospital, Barnes Hospital and also at the Homer G. Phillips Hospital. Much to our surprise, in many of the patients who were admitted with vague abdominal symptoms, increased diastase readings were obtained and recorded. It is also interesting to note that many cases other than pancreatitis showed an increased diastase, namely, such conditions as intestinal obstruction, acute appendicitis and perforated duodenal ulcer.

The findings were recorded and we noted that the average normal individual had a diastase reading of between 75 and 150 Somogyi units, and this recording was taken as our normal. Increased diastase readings above 1,000 units were taken to indicate possible involvement of the pancreas. This in turn, of course, guided our treatment, which up to that time had given very unsatisfactory results. Now, I do not mean to say that every elevated diastase indicates acute pancreatitis. As I mentioned before, there are other conditions which may be associated with this elevation, and one must not forget that this is only a

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laboratory test. We are particularly suspicious of any diastase that is over 1,000 units, using that more or less as an established level, although we have found many cases of proven pancreatitis whose diastase has been less than 1,000 units. Again I repeat, the clinical picture must be evaluated. In general an individual who has any abdominal symptoms whatsoever in whom you find an increased diastase of 1,000, 2,000 or 3,000 units, or higher, one must be very, very suspicious of acute pancreatitis.

Very important in the use of this test is the time that the blood is drawn. We are so equipped at the Jewish Hospital, at Homer G. Phillips Hospital and at Barnes that blood can be drawn at any time during the 24-hour period and the test performed. The best time to draw blood for diastase is as soon after the onset of the attack as possible, for one may find that in a period of four to six or eight hours the diastase may drop precipitously. You may find the patient

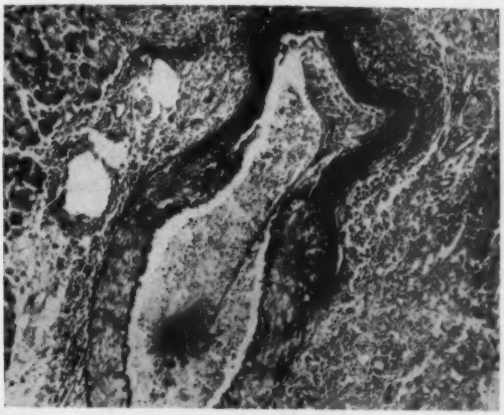

Fig. 1—Pancreatic artery, elastic tissue stain, mag. approx. 250x. The upper portion of the artery shows necrosis of the wall including an abrupt interruption of the internal elastic membrane. The latter is due to the pancreatic enzyme "elastase".

to have a diastase of 2,000 or 3,000 units one hour after the onset of attack and six to eight hours later have a diastase of only 3 or 4 hundred. This, of course, is very confusing and one begins to wonder if there is something present other than the pancreatitis. I should like to call your attention to the use of the urine diastase if one suspects that the patient has pancreatitis and that the diastase probably has been missed in the blood at its highest registration. I would suggest that a diastase follow-up be done on the urine for, as you know, the diastase may be elevated in the urine as late as two or three days after the blood level has returned to normal.

As to the etiology of pancreatitis, I am not going to go into all the phases of etiological factors that have been given; probably the one most familiar to

all of you is the common channel theory which Opie propounded many years ago. While many workers feel that most cases arise on such a basis, we have been unable to account for more than 20 per cent of the cases of pancreatitis as related to biliary tract disease.

Pancreatitis, we believe, is a disease which may have many causes, infectious, allergic, obstructive, toxic, hormonal, traumatic (including postoperative), vascular and possibly others. Basic to our concept is the consideration that the pancreas is capable of self-digestion because of the proteolytic and lipolytic enzymes which it makes. Protective factors are present also in the form of mucins, inactive enzyme precursors and antienzymes. Any situation which removes protective factors or activates enzymes may lead to pancreatic digestion or pancreatitis. We have been particularly interested in vascular factors which may affect either enzyme activation or loss of protection. It has been shown that necrosis anywhere may lead to the activation of trypsin in the pancreas, hence vascular occlusion with infarction may be an initiating event. Such occlusion and infarction in the pancreas is a much more frequent event than is generally recognized, hence vascular disease of the pancreas may be important. The extensive hemorrhage which occurs in some cases of pancreatitis, we believe is due to the activation of elastase. This enzyme dissolves away the elastic fiber of arteries and veins, thereby causing their rupture and hemorrhage. It is pertinent that the pancreas has its maximum elastase content in the age period 40-50, when most cases of hemorrhagic pancreatitis occur.

Figure 1 shows the digestion of the elastic membrane in a portion of the vessel which projects into a necrotic area. As regards vascular factors, it is also pertinent that the greatest number of cases of pancreatitis occurs in the same age bracket in which we have the largest number of coronary occlusions, and other R.V.D. between 40 and 60 years.

A final word as to protective factors. The pancreas contains an extremely high concentration of calcium, probably the highest of any organ in the body other than the bones, and it is known that calcium is an inhibitor of trypsin. Recent studies on the occurrence of pancreatitis with parathyroid disease are extremely interesting, and further study along these lines may yield an important clue in the etiology of this disease.

So-called chronic pancreatitis, we believe, represents a variety of antecedent conditions of the pancreas. It may result from repeated bouts of acute pancreatitis, from a continuing low-grade, subclinical inflammatory disease, or from a progressive fibrotic disease on a metabolic basis. We have called this cirrhosis of the pancreas, not only because in its end-stage it gives a hard, nodular pancreas similar to that seen in a cirrhotic liver, but because it has parallel etiologies and comparable pathologic changes.

While we place much stress in some of the cases on metabolic (alcoholic) factors, on dietary indiscretions and on the common channel theory with stone,

yet recently, we have reported six cases at the Jewish Hospital in which we have found pancreatitis in the newborn, and in one case, we are sure, *in utero*. Surely, one cannot attribute the cause of pancreatitis in cases of this kind to the more commonly accepted etiologies.

Clinical Aspects of Pancreatitis

The clinical picture of pancreatitis is one which may be very confusing. The typical frequent pain, nausea and vomiting, etc. do not necessarily have to be present. Pain was a major symptom in over 90 per cent of the cases in our present series. It is often described as a sudden agonizing persistent colicky or stabbing pain. Again I repeat, this does not have to be the rule, and it usually is in the obscure case where we do not have this so-called typical picture that the pancreatitis is so frequently missed. The pain may be continuous, it may be paroxysmal in character, it may be a very dull pain, and sometimes so severe that the patient is actually in shock. The severity of the pain is often considered a rough index of the degree of pancreatic hemorrhage. This is not necessarily true. Frequently the pain is so mild as to be completely overlooked and not even considered. This we have seen in many cases where the pancreatitis, particularly, was found at postmortem after such operative procedures as transurethral prostatectomy, gastrectomy and other surgical procedures. Nausea and vomiting frequently follow the pain and in our series was found in about 40 per cent of the cases. Abdominal distention is a common symptom of acute pancreatitis and frequently due to the paralytic ileus which follows in the course of the disease. Shock is present in the more severe types of the disease and a drop in blood pressure often accompanied by cyanosis and dyspnea also occurs, presumably due to associated coronary insufficiency.

It has been our experience that the individual who comes in with a picture of shock is frequently one that we see associated with a massive hemorrhagic pancreatitis. (This is not always true.) Temperature may be mild or absent, ranging from 100°, sometimes as high as 102° and 103°. Icterus may be encountered, particularly if the pancreatitis is associated with a biliary colic due to calculi, or if the edematous process around the common duct and sphincter of Oddi becomes severe enough to cause obstruction.

Findings in an Acute Pancreatitis

First, the abdominal findings are usually associated with tenderness on palpation corresponding to the site of pain. This is usually located in the epigastrium. One may find spasm of the abdominal muscles and at times none can be found. If the disease progresses in spite of the treatment, all of the above symptoms seem to progress, ileus becomes more prominent, tenderness is associated with a well defined muscle guard in the area involved, usually the upper abdomen. X-ray studies at this time will give further evidence of ileus and perhaps the distended loop which is so frequently sought, looked for and found.

While we know that ascites of the abdomen takes place, it is rather difficult to elicit at this time. As noted by Cullen and Hofstetter, ecchymoses above the umbilicus, hemorrhage in the flanks (Turner's sign) may appear. But this has been rather rare in our experience.

Laboratory findings constitute the basis for the diagnosis of acute pancreatitis in many cases. Often the definitive diagnosis rests on the demonstration of elevated enzyme levels in the blood and in the urine. We have had little or infrequent experience with the serum lipase. The amount of amylase released in the urine and blood are determined by the access of the released enzyme to the vascular system of the pancreas. In those cases in which pancreatitis is on the basis of a vascular occlusion, or vascular rupture, the pancreatic circulation is seriously impaired and it may be that the released enzymes are unable to gain access to the general circulation. It may also interest you to know that at times we were unable to find a direct correlation between the level of the serum amylase and the intensity of the pancreatic process.

There are other findings that I will mention briefly. There are sometimes electrocardiographic findings and occasionally x-ray findings. X-ray of the abdomen frequently shows the ileus and a distended duodenal loop. Also in several of our cases there were pleural effusions which on tapping showed a high diastase level.

Now, what is the clinical course of acute pancreatitis? In the early stages we cannot be clinically certain which way the disease is going to proceed. We believe that there are four different clinical types of pancreatitis: 1. The acute edematous pancreatitis, which if uncomplicated will typically run its course in two or three days after the onset, followed by prompt recovery. 2. Acute necrotizing pancreatitis may at first appear deceivingly mild, particularly if progression of the disease is through a stage of acute edematous pancreatitis. If the patient fails to improve after several days and signs of intraabdominal inflammation persist, or become intensified, it is then likely that parenchymatous necrosis has taken place. This type may go on to death, or may be delayed for two or three weeks, when the secondary complications of pancreatitis may present themselves. 3. Acute suppurative pancreatitis may develop as a result of secondary infection following on the preceding forms of the disease. These patients become extremely toxic, with high fever and manifestations of infection may completely mask the symptoms of pancreatitis. Suppuration may begin a day or two following the onset of the disease, but is more often first detected after five to seven days. 4. The hemorrhagic forms of pancreatitis if sufficiently severe will reveal a significant state of shock and abdominal findings as described above. They may be present at the onset; the precipitating factor is a vascular rupture as in pancreatic apoplexy.

The differential diagnosis involves such conditions as: 1. acute cholecystitis, 2. perforated peptic ulcer, 3. acute intestinal obstruction, 4. acute appendicitis,

5. any generalized peritonitis, 6. acute coronary occlusion, 7. dissecting aneurysm of the aorta; and the rarer conditions such as renal colic, splenic rupture, pneumonia, and mesentery thrombosis. The clinical manifestations and the complications of acute pancreatitis may occur during an attack of acute pancreatitis, with no antecedent history, or during an acute exacerbation of chronic pancreatitis.

What are the complications that may occur? First, true abscess formation, which forms as a result of areas of liquefaction, necrosis.

In our series of cases 10 per cent presented this picture (Fig. 2). Two, pseudocyst formation. Although this form was a rare complication in our series, I have personally been able to follow 15 such cases, which I have previously reported. Symptoms of pseudocyst result from pressure exerted by the pseudo-

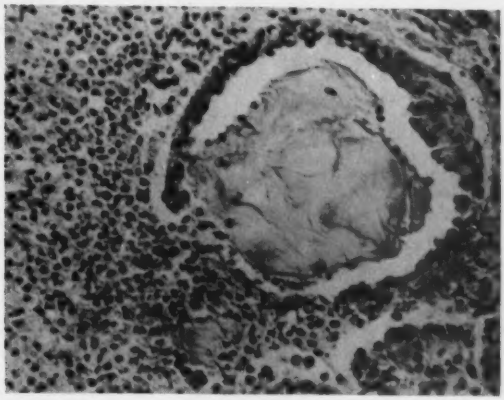

Fig. 2—Pancreas, hematoxylin-eosin stain, mag. approx. 250x. A large pancreatic duct, partially destroyed and containing inspissated secretion, lies in an abscess cavity composed of polymorphonuclear leucocytes.

cyst on the stomach, duodenum and bile ducts. The most reliable single clinical feature is the presence of an upper abdominal mass. The mass is usually deeply placed, rounded and does not move on respiration. A cyst arising in the tail of the pancreas may be surprisingly mobile. With the progress and development of a pseudocyst during an attack of pancreatitis, serum diastase values are often in excess of 1,000 Somogyi units; at other times titers are usually around 200 to 300, often within normal limits. By far the most valuable diagnostic tool is radiography followed by a barium meal. Lateral view will definitely show the distortion of the adjacent viscera.

If the contents of the pseudocyst remain sterile, there will be no systemic reaction, but if bacteria become established abscess formation occurs. These are the most prominent and most frequent complications that we have seen,

although there have been others in other institutions such as biliary obstruction and fistula formation. We do not use cholecystography in the cases of acute pancreatitis to determine whether or not there is any biliary tract disturbance, such as calculi, for at least a period of two or three weeks. We have found that when this is done at an earlier date it is completely unsatisfactory, and if repeated two to three weeks later one may find a completely opposite finding.

One significant factor in the so-called hemorrhagic pancreatitis, which might be a warning or a sign of the seriousness of the disease, is a drop in the blood calcium. This has been found by many authors and a calcium determination should be done routinely in every case of pancreatitis.

Regarding the treatment of acute pancreatitis, for the acute phase the treatment in our opinion is completely conservative. This is differed with by some of our colleagues who are close at hand to our institution. We continue to feel that in the acute phase of acute pancreatitis surgery is not indicated. Surgery, in our opinion, is indicated for the complications which I mentioned previously.

What should one do in the case of acute pancreatitis? First, relieve the pain. Because of the knowledge that morphine and associated drugs produce spasm in the sphincter, we have used Leriton, Demerol and codeine. We have not had much success with the paravertebral block, nor have we used epidural anesthesia. Inhalation of amyl nitrate has been suggested by such men as Doubilet and Mulholland for the release of spasm of the sphincter of Oddi, but in our experience it has not given the satisfactory results that others have obtained. For the treatment of shock, which consists of hypotension, decreased blood volume and hemoconcentration, transfusions of whole blood, the administration of 1 to 200 mg. of 25 per cent normal human serum, and albumin solution seem to have a very favorable effect on these patients. Cantwell and Wells believe that the serum albumin when administered has an antitryptic activity. This is not accepted by many others. Secondly, continuous suction should be instituted. Third and very important in the treatment of the acute phase is the replacement of fluids and electrolytes. Part of this has already been covered in the treatment of shock. Because of the great loss of sodium, potassium and chloride concentrations, we have been in the habit of using lactate and Ringer's solution. Attention must be drawn to the fact that not only must there be replacement of the initial loss of fluid, but also, that resulting from the continuous nasal gastric suction which is highly important in this treatment. Potassium loss may be gauged by the electrocardiographic changes, and the loss of calcium at times is so great that we have frequently used 10 to 20 c.c. of a 10 per cent solution of calcium gluconate once or twice daily.

The temporary suppression of pancreatic secretion is accomplished mainly by the gastric suction. This treatment should be instituted early, maintained as long as indicated, with periodic changings of the tube. For this we use a soft

rubber or polyethylene tube. For the prevention of suppurative pancreatitis, which may develop initially on an infectious basis, or it may develop later, we have adopted prompt early vigorous use of antibiotic therapy in almost all cases of pancreatitis. The antibiotic therapy we have used is mainly the penicillin procaine intramuscularly, 600,000 units every 12 hours, providing the patient is not allergic to the drug, along with chloramycetin either intravenously or intramuscularly. Under this procedure of treatment the harmful interstitial edematous pancreatitis will, in a great number of cases, go on to repair or resolution, some without further attacks and some with continued attacks. If during the acute period of the initial attack we are unable to ascertain the cause of the pancrea-

Fig. 3—Gross specimen of pancreas several years after cystogastrostomy. A small cyst cavity at the bottom of the illustration is all that remains of a large pseudocyst.

titis after complete subsidence of the acute phase, we then proceed to make an effort at pinpointing the etiology if possible.

Now for the complications of pancreatitis; these become chiefly surgical, namely, the pseudocyst formation and abscess formation. These may occur early during the most acute phase; we having seen some occur as early as six weeks, the latter being a continuation of the acute phase, and others occurring as late as two, three and four months after the acute phase has subsided. Treatment of abscess formation is of course, laparotomy, drainage of the abscess and, as we have seen in one or two of our cases, the removal of a complete slough constituting almost the entire pancreas itself except the head.

(Slide) The treatment of pseudocyst is controversial and I should like to say that the excision of the pseudocyst in my hands has been most difficult, for,

as you will recall, the cyst has actually no cyst wall. Marsupialization may be carried out, although this is a prolonged procedure. The content of the cyst usually contains a very high diastase level, running as high as 7,000 to 8,000 units. Whenever possible, in our hands, providing the cyst is posterior, and particularly attached to the posterior aspect of the stomach, we have leaned toward the drainage of the cyst into the stomach by simple entrance into the posterior wall of the stomach. Our results with this procedure have been very favorable with the exception of one case. If one examines the anastomosis ten days after the operation has been carried out, it is surprising to see how little if any of the cyst can be observed by x-ray examination. Here I have a slide showing a case in which the individual died of a coronary occlusion one year after such a procedure, and one can hardly identify any connection between the pseudocyst and the stomach which had been made the year before (Fig. 3).

We have already spoken of our concept of the nature of so-called chronic pancreatitis. The treatment of chronic pancreatitis in our hands has been variable and not too successful. We have not been too impressed with cutting of the sphincter of Oddi; in fact, we have seen instances where this has been done and the patient continued to have acute attacks of pancreatitis. Our operative experience in chronic pancreatitis is very limited because of its infrequency at Jewish Hospital. The best results have been in one or two cases in which most of the pancreas has been removed in an effort to find the pancreatic duct for posterior drainage, as described by Puestow. I cite one of the cases that to us was most remarkable.

In conclusion, let me say I hope I have hit the highlights of the subject in the few moments allotted to me. This has become such a very popular and large field of investigation, much is yet to be found in an effort to clear the scene.

Discussion

Dr. Paul Mecray, Jr. (Camden, N. J.):—I'm pleased to have the opportunity of hearing Dr. Probstein and Dr. Blumenthal's encyclopedic paper.

It follows quite closely data collected in their book, which book I recommend to any of you who have not read it.

I have reviewed the experience of acute pancreatitis and pancreatitis in South Jersey, the land of apple-jack and high consumption of alcohol. I, however, have no intention of boring you with any statistical analysis of this material.

Somehow I feel it is rather curious that you should ask a surgeon to discuss Dr. Probstein's paper because the primary disease about which he talked, acute pancreatitis, is still in my mind a medical disease.

Unfortunately, however, we as surgeons stumble into or sometimes are led into operating on some of these cases through mistaken diagnosis.

Dr. Probstein in his book expresses very strongly the opinion that nothing should be done at this time. We have taken a quite different point of view and find that once we are there that we shall do a relieving procedure.

I frankly do not think and cannot see, in going over our cases, that such a procedure has increased our mortality. I have the impression that it has probably improved our mortality.

As surgeons, however, once we have opened these patients, you can rest assured that we obtain the services very promptly of one of our gastroenterologists who is particularly interested in the disease of pancreatitis, to help manage the patient with us.

I have always had, in the past, the philosophy that when we do a sphincterotomy, that it probably closed sometime later. I have had the opportunity now over the years of seeing postmortems on five patients on whom I have done sphincterotomies from one to nine years previously, all of which were completely open.

I expressed great surprise at that finding. I do not try and inform you, however, that all of these patients were free of attacks of recurrent pancreatitis as a result of my procedure.

Frankly the problem of recurrent attacks of pancreatitis in the alcoholic which is the group we seem to see so often, is to me a completely unsolved disease.

PEPTIC ULCERS INDUCED IN WHITE RATS BY RESERPINE AND STRESS

The Protective Action of Roterized Bismuth Subnitrate

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The first official communication on bismuth was delivered to the *Academie des Sciences de Paris* in 1753. In 1803 Odier[1] employed bismuth internally. In Brussels, in 1847, Daumerie[2] addressed the *Society of Medical and Natural Sciences* almost with prophetic wisdom: "Even though bismuth treatment (diseases of the stomach associated with stimulation of the central nervous system) has no intrinsic value in the eyes of many scientists, we are convinced it is of value and wish to call the attention of physicians to a substance which it would be wrong to ignore."

By purely experimental methods, the pharmacological results reported in this paper clearly confirm the empirical opinion defended by Daumerie more than a century ago.

Clinical Considerations

Bismuth subnitrate is one of the drugs presently used in the treatment of peptic ulcers. It supposedly coats the crater of the ulcer and in this manner offers mechanical protection[3]. Bismuth subnitrate was official in U.S.P. XII but was omitted from U.S.P. XIII in 1947 and is presently recognized in the *National Formulary* (N.F. XI, 1960) and in the *International Pharmacopoeia.*

In 1957 successful use of a unique form of bismuth subnitrate, processed by roterization so as to produce a colloidal suspensoid, was reported in American medical literature[4]. In a series of 155 cases of gastric and duodenal ulcer, there was immediate relief of the pain in 92 per cent of cases and roentgenological healing of the ulcer in 81 per cent*.

A later study of this medication, used in the treatment of the ulcer syndrome, showed effective relief of epigastric pain and discomfort, heartburn, flatulence, gas bloating and anorexia. The therapeutic results were attributed most significantly to the specially processed bismuth subnitrate[5].

In a group of 98 ulcer cases studied in Scotland, with an average duration of 12 years, there was a satisfactory therapeutic response after one month's treatment with roterized bismuth subnitrate in 90 per cent of cases and the average incidence of relapses was reduced 82 per cent[6].

*Supplied for the investigation as Romach tablets (known in Europe as Roter tablets) by ROR Chemical Co., New York, N. Y. Manufactured by Pharmaceutische Fabriek Roter, Hilversum, Holland.

Several other reports have confirmed the value of roterized bismuth subnitrate for peptic ulcer on a clinical basis[7-10].

Pharmacological Background

This pharmacological study is derived from the experimental research work performed by Prof. Jean La Barre and his collaborators in the Laboratory of Pharmacodynamics, University of Brussels, Brussels, Belgium.

Since bismuth subnitrate probably owes its therapeutic effect to its purely physical property of adhering to the gastrointestinal mucosa and the crater of

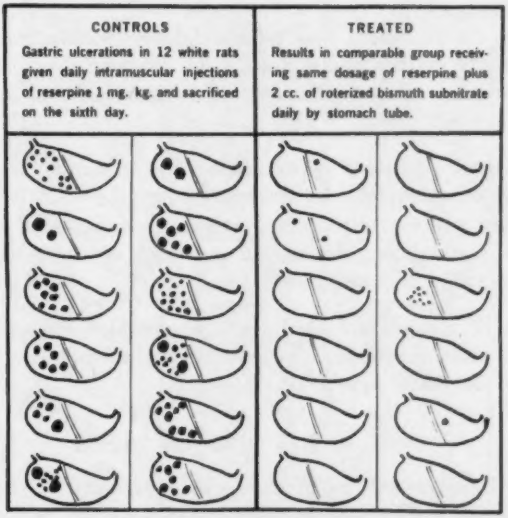

Fig. 1—Prevention of reserpine ulcers.

the ulcer, it is important to compare the protective properties of roterized bismuth subnitrate with those of the ordinary salt.

It is known that reserpine produces a marked increase of gastric mobility and acidity in rats, mice, cats and dogs[11,12]. Considerable hyperacidity following use of reserpine has also been observed in man[13], and this effect is not influenced by previous administration of atropine[14]. The increased secretory activity of the stomach apparently leads to exacerbation of co-existing peptic ulcer[15,16]. Recurrence of peptic ulcer with bleeding may be produced by reserpine[17-19].

In a previous pharmacological study[20] it was shown that gastric hypersecretion, hyperacidity and severe ulceration occur in the stomach of a dog with a permanent gastric fistula following reserpine. Subsequently it was established

that this secretory response is of parasympathetic origin, since it can be prevented by prior administration of atropine[21].

The occurrence of hypersecretion, hyperacidity and ulcer formation in the rat's stomach following use of reserpine was confirmed[22]. This pharmacological procedure was used in order to compare roterized bismuth subnitrate with bismuth subnitrate N.F.

The severity of the ulcer provoked by reserpine in rats is mainly due to the parasympathetic effect of the alkaloid[23]. The fact that antiserotonin and antihistaminics do not influence the development of the ulcer lesions suggests that serotonin and histamine are not etiological factors.

It has been demonstrated that roterized bismuth subnitrate adheres more closely to the gastric mucosa and is much more effective than bismuth subnitrate N.F. in protecting rats from experimental ulceration induced by ligation of the pylorus (Shay method[24-25]).

In experimentally induced peptic ulcers (by histamine in oily solution in rats and by hydrochloric acid solution dripped into the stomach in guinea pigs) roterized bismuth subnitrate promoted active granulation of the ulcer areas, re-epithelization and healing. Ulceration persisted in the controls and 35 per cent of one group died of perforation[26].

The object of the present study was to conduct similar experiments on white rats with induced ulcers more comparable to those occurring clinically in man, namely, following reserpine and stress.

Prevention of Reserpine Ulcers

Extensive ulceration can be produced in white rats weighing 150-180 gm. by daily intramuscular injections of reserpine in a dosage of 1 mg. per kilo for four to five days.

The experimental animals were divided into two groups, each composed of two series of 6 rats. One group (controls) was given a daily intramuscular injection of reserpine 1 mg./kg. The other group was given the same dosage of reserpine together with a daily oral dose of roterized bismuth subnitrate 2 c.c. by stomach tube.

On the sixth day all animals were sacrificed and their stomachs were examined to determine the number and extent of ulcerations. The results are shown in Figure 1.

Figure 1 shows that concomitant administration of roterized bismuth subnitrate protected the animals almost completely from the ulcerative lesions of reserpine as demonstrated in the controls.

It can be concluded from these findings that in rats daily administration of roterized bismuth subnitrate will prevent the formation of reserpine-induced ulcers, provided that this treatment is started and continued over the same period as the reserpine injections.

These observations prove that roterized bismuth subnitrate is effective in preventing a particularly severe form of experimental ulcers located in the

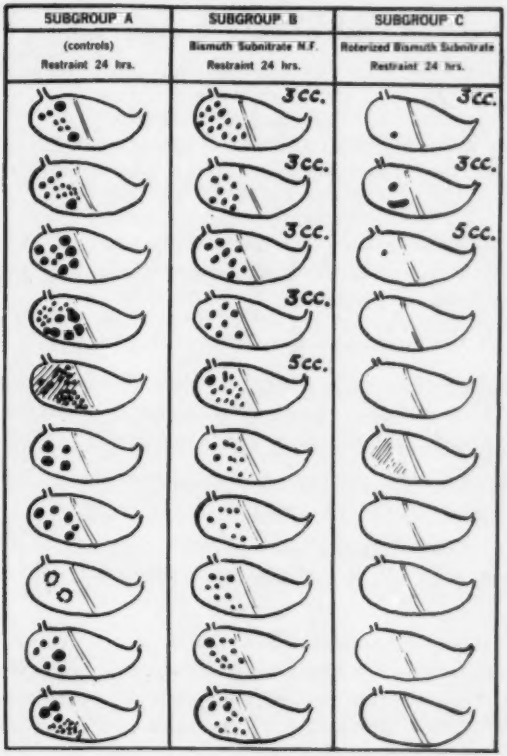

Fig. 2—Prevention of "stress" ulcers.

pyloric antrum of the rat's stomach, the site of the great majority of clinical gastric ulcers in man.

Prevention of Stress Ulcers

Emotional factors may play a most important role in the etiology of peptic ulcer, since the central nervous system through the vagus may produce hypermotility and hypersecretion of gastric juice[27]. The "stress" method[28] of inducing

gastric ulcers in white rats under restraint is therefore comparable to human conditions.

By the restraint method the animals are suspended for 18 to 24 hours in a metal corset, the paws and tail being immobilized by adhesive tape. After 24 hours the animals are sacrificed for postmortem examination of the stomach.

Using the restraint method, a controlled experiment was carried out on two groups of 30 white rats weighing 140-180 gm. The animals were divided into three subgroups, each of which included 10 rats.

In Subgroup A (controls) the animals were subjected to 24-hour restraint only with no medication.

In Subgroup B the animals received 3-5 c.c. of a 10 per cent suspension of bismuth subnitrate N.F. half an hour before starting the standard 24-hour restraint procedure.

In Subgroup C (treated group) the animals received 3-5 c.c. of a 10 per cent suspension of roterized bismuth subnitrate half an hour before starting the standard 24-hour restraint procedure.

The results of the experiment are shown in Figure 2.

In Group A (the controls), where the animals were subjected to 24-hour restraint only, all 10 stomachs examined postmortem showed severe ulcerative lesions, frequently of a crateriform or hemorrhagic nature.

In Group B, where the animals received 3-5 c.c. of a 10 per cent suspension of bismuth subnitrate N.F. half an hour before the 24-hour restraint procedure, all 10 stomachs examined postmortem showed severe crateriform and hemorrhagic ulcerations, although the lesions were somewhat less advanced than in the controls.

In Group C, where the animals received a 10 per cent suspension of roterized bismuth subnitrate half an hour before the standard 24-hour restraint procedure, there was complete protection against ulceration in the 8 animals which were given 5 c.c. and marked attenuation of the lesions in the 2 animals which received 3 c.c.

It was also noted that the 5 c.c. doses of bismuth subnitrate suspension left a slight retention of particles in the stomach after the 24-hour restraint period, but with the 3 c.c. dosage this retention did not occur.

We can conclude from the results of our experiments on over 90 rats that roterized bismuth subnitrate, with its special properties of adhesion and colloidal dispersion, protects the gastric mucosa from ulceration induced by "stress". In order to provide full protection, a dosage of not less than 4 c.c. per 160 gm. must be administered.

It was further noted that the gastric lesions provoked by stress are less severe than those which follow administration of reserpine.

Summary

The clinical success of roterized (colloidal suspensoid) bismuth subnitrate in treatment of peptic ulcers has been confirmed by three sets of pharmacological experiments on artificially induced ulcers in white rats.

First, in experimental gastric ulcers induced by the Shay method (application of pyloric ligation after 30 hours' starvation) prior oral administration of roterized bismuth subnitrate provided undoubted protection against the development of ulceration as compared with only slight reduction of ulceration when bismuth subnitrate N.F. was given.

Second, concomitant oral administration of roterized bismuth subnitrate prevented reserpine-induced ulcers almost completely.

Third, prior oral administration of roterized bismuth subnitrate in adequate dosage prevented "stress" ulcers completely (induced by 24-hour restraint). Ordinary bismuth subnitrate N.F. under the same conditions merely reduced the severity of the ulcerations.

The results of these experiments clearly demonstrate that there is a marked difference between roterized bismuth subnitrate and ordinary bismuth subnitrate N.F. in their power to protect the gastric mucosa of rats from all kinds of experimentally induced ulcers. In fact, bismuth subnitrate N.F. appears to be of little use in preventing the development of these ulcerative lesions.

The experimental results on artificially provoked peptic ulcers confirm the favorable clinical reports by American and European investigators.

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CARRAGEENAN IN THE MANAGEMENT OF PEPTIC ULCER*

A Preliminary Report

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Glen Ridge, N. J.

Although the etiology of peptic ulcer still remains to be elucidated, there is little doubt that both acid gastric juice and pepsin have an important role in this disease entity, which affects approximately 10 per cent of the world's population without regard for race or socioeconomic position. Thus, with current knowledge, the two most logical avenues of approach to the management of peptic ulcer would be the establishment of achlorhydria and/or the inactivation of pepsin.

Since most peptic ulcer regimens in present use are directed towards the reduction of gastric acidity and are far from satisfactory, and since the inhibition of pepsin has not been achieved, we were very interested in the recent studies

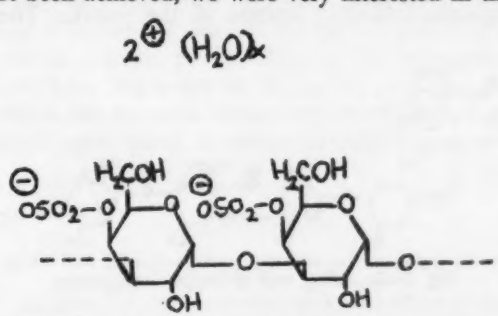

Fig. 1—Repeating unit of lambda Carrageenan.

on Carrageenan carried out by Houck and associates[1] and by Anderson and Watt[2]. These workers were able to prevent ulcerations in laboratory animals treated with Carrageenan. In an attempt to reproduce their encouraging results in humans, a clinical study on the use of this seaweed extract was carried out in peptic ulcer patients.

Chemistry

Carrageenan is an extract obtained from *Chondrus crispus* and *Gigartina mamillosa*, and is believed to be composed of two major fractions, kappa and

*Read by title at the 25th Annual Convention of the American College of Gastroenterology, Philadelphia, Pa., 24, 25, 26 October 1960.

The Carrageenan used in this study was supplied to us through the courtesy of G. Kenneth Hawkins, M.D., Department of Clinical Investigation, Schering Corporation, Bloomfield, N. J.

lambda. Their physical separation is accomplished through the ability of the kappa fraction to precipitate selectively in the presence of potassium ions. Carrageenan is thus a polysaccharide hydrocolloid composed of two distinct galactose sulfates. Both components are polydisperse with molecular weights in the range of 100,000 to 500,000. Carrageenan forms a mucilaginous substance when mixed with water and is believed to adhere to the stomach wall, thus providing a protective coating against acidity or pepsin.

It is interesting to note that the colloidal properties of Carrageenan have long been recognized, as may be seen by its extensive use in dairy products, puddings, baked goods, oil emulsions, toothpastes, hand lotions and, more recently, in frozen confections.

Pharmacology

Working with rats, Houck and his associates[1] achieved a substantial reduction in ulcers, induced through the use of Shay's technic, with the oral administration of Carrageenan following ligation of the pylorus. These investigators

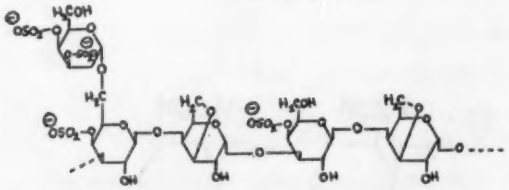

Fig. 2—Repeating unit of kappa Carrageenan.

also found that Carrageenan did not affect the gastric pH, but appeared to act as a competitive pepsin inhibitor. Anderson and Watt[2] were able to protect guinea pigs against acute peptic ulceration of the stomach and the duodenum with this seaweed extract. Code and his collaborators[3] made similar observations in dogs with ulcers induced by massive doses of histamine in beeswax.

Materials and Methods

Carrageenan was given to 22 peptic ulcer patients, 17 males and 5 females, ranging in age from 26 to 69 years. This series comprised 20 duodenal ulcers, one gastroenterostomy and one marginal ulcer; clinical diagnosis of peptic ulcer was confirmed by x-ray findings in every case. The preparation was administered orally in the form of powder containing 10 per cent of the active material and 90 per cent sugar; this powder was dissolved in drinking water. Thirteen of these patients received Carrageenan as the sole medication, while nine were given anticholinergic and/or antacid preparations concomitantly. Patients were examined at regular intervals during treatment. In order to determine the degree

of pepsin inhibition produced by Carrageenan, gastric juice samples of 5 patients were assayed both by the Mett Tube and the hemoglobin method[4].

Results

An evaluation of the 22 cases treated with Carrageenan shows that, of the 13 patients receiving the Carrageenan powder alone, five experienced good symptomatic improvement as reflected by a feeling of relief from burning, pain and gas; these patients also showed increased weight gain. Of the nine patients receiving Carrageenan and other medications, seven showed the same type of symptomatic improvement. Ten patients failed to show a measurable degree of improvement. With the exception of one case of dizziness there were no side-effects attributable to Carrageenan. Laboratory analyses of the gastric juice samples of 5 patients failed to show significant inhibition of pepsin.

Summary and Conclusions

Our results in this small series of peptic ulcer patients suggest that the favorable findings in laboratory animals are not reproducible in man and that Carrageenan is not an effective pepsin inhibitor. The improvement seen in some patients may have been the result of the ability of Carrageenan to coat the stomach wall. While this seaweed extract may be of some help in the symptomatic treatment of peptic ulcer, it cannot be relied upon to produce clinical cures.

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EVALUATION OF A NEW COMPOUND FOR CHRONIC CONSTIPATION

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Introduction

It has been suggested by some that constipation is the most common of all physical complaints[1]. It is therefore only undertsandable that such a universal problem as this would be accompanied by a various assortment of diversified treatments derived from folklore, superstition, and of course from sound medical knowledge.

The logical attack in any medical problem is first to arrive at a diagnosis, second to discover the etiology, and third to plan a regimen of treatment that will directly influence the etiologic factor. So it is with the problem of constipation. The diagnosis of this condition is obvious, for it invariably comprises the chief complaint which the patient presents.

Determination of the etiology is somewhat more difficult to ascertain. Lack of sufficient roughage, poor diet, emotional factors, spastic or irritable colon, poor habit training, or an atonic colon are all common etiologic factors[2].

It is only logical that the best approach to this problem is to rectify the poor diet, the spastic colon, or whatever is pertinent to the particular patient concerned. Although the treatment of these patients is usually quite effective, it is the patient who either does not present with any of these etiologies, or who does not respond to their correction if they are present, that presents the real problem in the treatment of constipation. It is for this group that all the various types of laxatives have been prepared. These latter usually fall into one of three main classes, viz., bulks, irritants, and lubricants.

The undesirable factors associated with the bulk-type of laxative are the difficulty in administration and the large volume of water intake required with the concomitant bloated feeling. Derivatives of the irritant cathartics are the harshness of treatment and the inevitable problem of rebound constipation. The lubricants, as exemplified by mineral oil, also leave much to be desired. In addition to anal leakage they often result in a decrease in absorption of vitamins and other nutrient materials. Flatulence often accompanies their use.

Recently, a new compound, Doxidan® (Lloyd Bros., Inc.) has become available for general clinical evaluation.

This compound produces a pronounced fecal softening effect with mild peristaltic stimulation—a combination that is regarded by many to be the most satisfactory form of anticonstipation therapy. This is based on the principle

that a much milder laxative agent can be fully effective in small dosage when it can stimulate the bowel musculature to act upon a softened, malleable intestinal content.

Since the whole purpose of this adjunct to fecal softening is to aid evacuation, the ideal agent would be one which acts solely on the lower bowel with the least possible irritation. It is apparent therefore that such a combination of fecal softening and peristaltic stimulation offers the best approach to the ideal laxative.

Doxidan combines the mild peristaltic stimulant, 1,8-dihydroxyanthraquinone (Danthron) with the advantage of a new fecal softener, calcium bis-(dioctyl sulfosuccinate). This new surfactant appears to offer markedly increased

TABLE I

AGE AND CONSTIPATION ETIOLOGY

Age (years)	Drug	Diet	Illness	Spasm	Atonicity	Postop.	Incidental	Total
Less than 20	—	—	3	—	—	—	2	5
20-29	1	1	6	1	1	1	5	16
30-39	—	—	10	4	1	—	20	35
40-49	—	—	10	2	1	—	13	26
50-59	—	—	2	—	—	—	2	4
60-69	—	—	4	—	1	—	—	5
Total	1	1	35	7	4	1	42	91

wetting and penetrating characteristics over other presently used agents of this type.

This report will discuss the general pharmacology of Doxidan and an evaluation of its use in cases of chronic constipation.

PHYSIOCHEMISTRY

Calcium bis-(dioctyl sulfosuccinate) resembles the older dioctyl sodium sulfosuccinate in most of its physical properties. It is neither absorbed nor chemically altered in the intestinal tract and exerts its effects solely through physiochemical action. It has been demonstrated that the 40 dynes per cm. interfacial tension at a mineral oil-water interface can be reduced to about 6 dynes per cm. at a concentration of only 0.035 per cent calcium bis-(dioctyl sulfosuccinate). This reduction compares with a value of approximately 14 dynes per cm. by the older dioctyl sodium sulfosuccinate at the same concentration. In fact, approximately three times as much of the older compound is necessary to achieve the

same effectiveness in reducing interfacial tension. It is indicated, of course, that it is this detergent action of reducing interfacial tension between water and the fats and oils in the intestinal contents that produces the fecal homogenization[2].

Dosage and Toxicity

Doxidan is supplied in bottles of 30 and 100 maroon soft gelatin capsules, each containing 50 mg. Danthron (1,8-dihydroxyanthraquinone) and 60 mg. calcium bis-(dioctyl sulfosuccinate). It is recommended that one or two capsules be administered to adults and children over 12 years of age, and one capsule be administered to children between the ages of 6 and 12 years, at bedtime, for two or three days, or until bowel movements are normal.

Calcium bis-(dioctyl sulfosuccinate) shares the general toxicity data for dioctyl sodium sulfosuccinate. Toxicity studies in animals and man have shown no evidence of acute or chronic toxicity for either compound[3,4,5]. Single doses as high as 50 mg./kg. body weight of the latter have been given to infants and

TABLE II

Patient's Activity and Results of Therapy

Activity	Number of patients	Average duration of treatment (days)	Average bowel movements per day
Active	35	4.8	2
Sedentary	1	4	2
Bed	55	4.8	1.6

3 gm. per day have been given to adults with no apparent ill effects. Chronic users of these agents have displayed no unusual reactions and studies have shown that there is neither inhibition nor improvement of the absorption of nutrients from the intestinal tract[2].

Side-effects

The administration of Danthron with fecal softening agents, as in Doxidan, only rarely results in the occurrence of bothersome side-effects. This has been repeatedly demonstrated by clinical studies comprising large numbers of patients. In fact, many studies report the complete absence of side-effects[2,6,11]. Such side-effects as do occur consist essentially of cramps, vomiting, and flatulence. No allergic reactions have as yet been reported.

Indications for Use

In one study a fecal softening agent combined with Danthron, as in Doxidan, was administered to over 200 patients with chronic functional consti-

pation, severe temporary constipation, or spastic constipation. Many of the chronic patients had been afflicted with this disorder for over 20 years. All of these patients displayed a marked softening in the stool consistency with elimination of the need for additional laxatives and enemas. It was only in rare cases that the constipation reappeared upon withdrawal of the drug. Side-effects were rare and these were of the insignificant nature already described. In close to 170 of these patients this combined therapy was effective and was withdrawn in eight weeks[10].

That the problem of constipation in infants is quite common, is well known. Most of these children present with an atonic type of constipation due to previously administered cathartics, enemas and suppositories. Conditions such as Hirschsprung's disease, rickets, hyperthyroidism, malnutrition, and anemia, are often the underlying causes in these constipated children—conditions which

TABLE III

Evaluation of Therapy and Patient Acceptance

Results	Patient acceptance	Correction of constipation
Excellent	54	56
Good	32	25
Fair	5	7
Poor	—	3

usually cause a decrease in peristaltic movements and general bowel muscular tonus[12].

Treatment with fecal softening therapy in infantile constipation is usually quite good. For example, with the less effective dioctyl sodium sulfosuccinate, treatment for 15 days has been reported to be sufficient for most of the usual problems of this type[13].

It is well known that constipation is a frequent complaint during pregnancy. When this problem arises as a result of the pregnancy itself it can usually be rectified by standard nontherapeutic measures. It is the patient who suffered from chronic constipation prior to her pregnancy that presents a therapeutic problem. The etiology of the constipation in these pregnant women is compression of the colon due to the progressively increasing pressure within the abdominal cavity. An atonic type of constipation is thus produced.

A combination of Danthron and fecal softening agents has proven to be of value in maintaining a soft stool and reducing the number of required enemas[9,14]. This fact is of special value when the pregnancy is further compli-

cated by hemorrhoids since softened stools result in a marked decrease in the pain of defecation.

The importance of maintaining a soft and pliable stool is well known particularly in postoperative patients with anal atresia.

Fecal softening therapy has been successful in producing the effects described above without the production of the bothersome factors associated with other types of laxatives, and in combination with Danthron, as in Doxidan, has been found very useful in the effective treatment of constipation due to medical, postoperative, and geriatric immobilization[2].

TABLE IV

SIDE-EFFECTS

Side-effects	Number of patients	Per cent of series
Gas	20	22
Fullness	6	7
Cramps	5	5
None	60	66
Total	91	100

PRESENT CLINICAL STUDIES

Our clinical experience with Doxidan consists of a series of 91 patients. As is shown in Table I, the majority fell within the 30 and 50 years age group with the fourth decade being the most common. Nearly 40 per cent of these patients were suffering with constipation derived from an illness, while in only a few was a spastic or atonic colon considered to be involved.

All patients were treated according to the accepted dosage of one or two capsules per day. Fifty-five (60 per cent) of the patients were treated while they were resuming their normal activity, whereas 31 (34 per cent) were treated while they were confined to bed. No difference in the required duration of treatment was apparent in those patients confined to bed and those resuming their normal activity (Table II). Patients who were not immobilized during treatment averaged two bowel movements per day. In those who were confined to bed the average was 1.6 per day.

The patients' opinion of the drug action was used as a measure of patient acceptance. Sixty per cent of the patients reported the drug to be "excellent", while 35 per cent of them reported it to be "good". No patients considered the drug as being "poor". These figures correlate well with the results of treatment

as evaluated by the medical investigator. He reported results to be "excellent" in correcting constipation in 60 per cent of the patients and results to be "good" in 30 per cent. In his evaluation results were considered only "fair" or "poor" in about 10 per cent. The majority of the cases treated displayed no side-effects during therapy. Although 22 per cent noted an increase in the volume of expelled gas, this did not appear to seriously annoy any of the patients affected. Other rare complaints were the feeling of fullness and cramps. No allergic or toxic reactions were reported.

Summary and Conclusions

The clinical usefulness of Doxidan has been studied in a series of 91 patients who were suffering from acute or chronic constipation due to illness, spasm, atonicity, surgery, and other incidental etiologies. The effects of this drug in providing fecal softening and peristaltic stimulation have been discussed.

Patient acceptance was "good" or "excellent" in 95 per cent of the cases.

The results of the study further demonstrate that the correction of constipation was "good" to "excellent" in 90 per cent of the cases studied.

In our opinion Doxidan has proved to be a safe and effective compound for the treatment of constipation.

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A CLINICAL EVALUATION OF A NEW ANTIDIARRHEAL AGENT

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This study was initiated in order to evaluate the efficacy and safety of a new antidiarrheal agent, Lomotil*, in patients with diarrhea of diverse origin and nature.

The active principle in Lomotil is diphenoxylate hydrochloride, chemically described as 2, 2-diphenyl-4-(4-carboxy-4-phenyl-1-piperidine) butyronitrile ether ester hydrochloride. It is legally classified as a narcotic since it was found capable of preventing withdrawal symptoms in known narcotic addicts. The manufacturer states, however, that there is little or no evidence of any addiction potential in clinical use.

Each Lomotil tablet contains 2.5 mg. of diphenoxylate hydrochloride and the subtherapeutic amount of 0.025 mg. (1/2,400 grain) of atropine sulfate to discourage deliberate overdosage. This amount of atropine will exert no clinical effect but, if a considerable overdosage of Lomotil were taken in the hope of obtaining a narcotic reaction, the pharmacologic effects of atropine would appear. The addition of atropine also makes it practically impossible to extract the active principle for purposes of abuse.

Acute toxicity studies[1] of diphenoxylate hydrochloride revealed an oral LD_{50} of approximately 400 mg./kg. of weight of rats and 1,000 mg. in mice, demonstrating a high index of therapeutic safety.

In chronic toxicity studies[1] the drug was given to rats and to dogs for six and three months in doses of approximately 96, 24 and six times the daily therapeutic dose recommended for man. Hematologic studies revealed no significant differences between the treated and untreated groups and no gross pathologic or histopathologic changes attributable to the drug were found at autopsy.

Janssen, Jageneau and Huygens[2] found that diphenoxylate had a high degree of efficacy in reducing the rate of gastrointestinal propulsion and the rate of fecal output in mice and rats. By radiologic study in humans Demeulenaere[3] found that an oral dose of 10 mg. had an inhibitory effect on gastrointestinal

*Lomotil, brand of diphenoxylate hydrochloride with atropine sulfate, G. D. Searle & Co., Chicago, Ill.

motility for six hours and that a divided dose of 40 mg. inhibited gastrointestinal motility for more than 24 hours. Peremans[4] reported an inhibitory effect which lasted from 24 to 48 hours after an oral dose of 10 mg. to 15 mg.

With this background Lomotil seemed to warrant further appraisal. We were interested in trying it on a wide variety of diarrheal conditions, with particular attention to those of functional origin and to seek any adverse reactions including symptoms of addiction.

Method of Study

Our study originally included 57 patients with diarrhea of varied etiology. One patient with ulcerative colitis did not return for follow-up and is not included in this report. The patients had complete studies to rule out or to confirm organic disease of the gastrointestinal tract as well as other related ailments. Complete blood studies, urinalysis, x-ray studies where indicated, sigmoidoscopy and other laboratory work or diagnostic procedures were carried out for each patient. Most of the patients had previously received various antispasmodics and tranquilizers. Thus, Lomotil was being instituted for the most part after prolonged attempts with other drugs had failed.

Twenty-seven patients were continued on sedatives or tranquilizers during the study. No control of the diarrhea had been achieved previously with these medications, and it was expected that whatever results were obtained in this group would be attributable to Lomotil. The eight patients with ulcerative colitis and regional ileitis continued to take antibiotic, antispasmodic, or corticosteroid medication. Among the 22 remaining patients there were instances of diabetes, duodenal ulcer, hypogammaglobulinemia, peptic esophagitis, hiatus hernia, gastroduodenitis, cholelithiasis, malnutrition and vitamin deficiency. These conditions were being treated appropriately and apart from the diarrheal symptoms.

All were started on 2.5 mg. of Lomotil three times a day and 26 patients continued at that level. In 30 patients the dose was increased to 10 to 20 mg. daily. The dose for the one remaining patient was reduced to 5 mg. a day.

Observations

Efficacy:—Table I summarizes the results with Lomotil. "Excellent" refers to quick results with a marked reduction in the number of bowel movements. "Good" results is somewhat slower control or less of a reduction in the number of bowel movements. Almost 73 per cent experienced excellent or good relief of the diarrhea as opposed to 17 per cent who were unimproved.

Four of the ulcerative colitis cases were severe ones with the patients in poor general health at the time of treatment. Lomotil was tried for from three to 16 days. In one patient the dose was increased to 15 mg. a day without any

noticeable effect. Another patient became distended and bloated with obstructive phenomena after one week of therapy. X-ray studies disclosed an inflammatory obstructive lesion of the descending colon which probably was partially obstructed when treatment was initiated.

The remaining 4 cases of ulcerative colitis were in patients who had had their illness for many years, but had been relatively quiescent recently. Treatment was instituted for the acute recurrence and sigmoidoscopic examination confirmed the acute exacerbation of the disease. For a period of 3 weeks the dose was increased to 20 mg. daily for each patient, and was discontinued after there was no evidence of improvement, on sigmoidoscopic examination.

Excellent results were obtained in cases of postparathyroidectomy diarrhea, gastrogenic diarrhea, and postoperative regional ileitis. In the latter patient the

TABLE I

SUMMARY OF RESULTS WITH LOMOTIL

Diagnosis	Number of Patients	Results		
		Excellent	Good	Poor
Functional diarrhea	28	24	4	
Ulcerative colitis	8			8
Spastic colitis	7	4	3	
Postgastrectomy syndrome	4	2	2	
Drug-induced diarrhea	5	2	2	1
Miscellaneous	5	3	1	1
Totals	57	35 (61.4%)	12 (21%)	10 (17.5%)

most severely diseased segment of bowel had been resected about six months prior to this study. She was having from six to ten loose bowel movements a day with considerable pain. Lomotil was administered in 5 mg. doses three times a day, with a reduction in the patient's corticosteroid medication to approximately one-quarter of the former dose. Control of the diarrhea was achieved within three days with a reduction in the stools to two or three semiformed to formed movements daily and complete absence of pain. The dose of Lomotil was reduced to 2.5 mg. three times a day and after the seventh day there was no recurrence of the severe diarrhea.

The diagnosis of gastrogenic diarrhea was confirmed by tests showing absence of free hydrochloric acid. This patient also had diabetes and cholelithiasis. The diarrhea had been present for six years with periods of incontinence when the patient was unable to leave her house. On Lomotil therapy stools were

finally reduced to one normal movement a day. After five days on 2.5 mg. of the drug three times a day, other medications were discontinued except for the antidiabetic drug. After 12 days there were periods of occasional constipation which were relieved by Metamucil*. After 61 days Lomotil was discontinued, and since then the patient has not reported any recurrence.

The postparathyroidectomy patient had recurrent bouts of diarrhea which did not respond to the usual antispasmodics and antidiarrheal medication. Each episode would last for two or three weeks. With 2.5 mg. of Lomotil three times a day the diarrhea was controlled within 24 to 36 hours, each time it recurred.

The patient in the miscellaneous class who obtained only good results had a transverse colostomy for diverticulitis. Response occurred after 7.5 mg. of Lomotil. The initial dose, however, caused a mild headache and was reduced to 2.5 mg. twice a day whenever bowel control was required, usually two or three times a month. In order to prevent discomfort or diarrhea at social functions, the patient would take one or two 2.5 mg. doses of Lomotil. This satisfactorily served to regulate and normalize the bowel.

The other patient who did not respond to Lomotil therapy because of hyperthyroidism was relieved of the diarrhea after receiving several doses of I^{131}.

Safety:—Eight patients (14 per cent) experienced side-effects. The four patients who had a mild headache, were relieved by decreasing the dose, without decrease in the clinical efficacy of the drug. Another patient, a dentist who was taking 10 mg. of Lomotil daily, reported feeling tired while working. In three patients on the beginning of the drug, tachycardia developed for one day; although the 7.5 mg. daily dose was not reduced tachycardia disappeared spontaneously.

Lomotil therapy has been prescribed in 47 patients without any evidence of withdrawal symptoms. Twenty patients were taking from 7.5 mg. to 20 mg. of the preparation for up to two months. Twelve others took the drug for three weeks and the remaining 15 patients, for periods of from two to 16 days.

There has been no evidence of symptoms of addiction either in patients taking Lomotil continuously or in those taking it only when needed. The three longest continuous treatment periods range from two and a half to three months.

Fourteen of our patients were receiving barbiturates concomitantly with Lomotil for six days to 34 days, without evident symptoms of addiction.

Comments and Conclusions

We found Lomotil to be efficacious in a variety of patients. A review of Table I and the description of our miscellaneous classification will attest to this

*Metamucil, brand of psyllium hydrophilic muciloid, G. D. Searle & Co.

fact. It was interesting to note that patients with diarrhea of such diverse etiologies did so well on the drug. In this regard, two other cases are of special interest.

A female patient, age 57, with functional diarrhea complicated by hypogammaglobulinemia had been having eight to ten loose stools daily. Lomotil was administered in 2.5 mg. to 5 mg. doses three times a day for a total of three weeks. On Lomotil the movements decreased to one formed stool a day.

The other case concerns a 67-year old male who had had a subtotal gastrectomy over three years ago, followed almost immediately by recurrent attacks of the dumping syndrome and diarrhea. X-ray examination showed a normal functioning stoma with a deficiency pattern of the small bowel. Nilevar* with Lomotil was given for a period of three weeks because of poor nutritional state and to help maintain weight.

A satisfactory response to the drug was established three days after start of therapy. Excellent response was achieved after six to seven days. Lomotil was discontinued after 48 days of continuous administration at the 7.5 mg. level, but the patient was advised to resort to its use when necessary. This has occurred two or three times after stress and emotional upset. The current dose adequate to abort diarrhea is 2.5 mg. three times a day for two days. Our thoughts in this case are that Lomotil in the foregoing dose could be used for two to three days in dumping syndrome diarrhea.

It is interesting to note that Lomotil was equally effective in decreasing bowel motility regardless of the cause of the diarrhea, except in ulcerative colitis. We feel that the shorter periods of improvement in the acute diarrheas can probably be attrtibuted to Lomotil, since such cases of enterocolitis are more prolonged when untreated.

We have also found that small doses of 2.5 mg. three times a day are often highly effective. Only 29 patients required an increased dose and then to not more than 20 mg. daily. In one patient response was evident in just 12 hours and in ten cases only a two- or three-day course of treatment was sufficient to return the patient to normalcy. Even where the severity of symptoms had led to incontinence, the diarrhea yielded to Lomotil with normal movements by the fourth day. Because of the nature of the original disease, however, prolonged maintenance at least on a p.r.n. basis will be necessary in most cases.

In our patients with functional diarrhea sedatives and tranquilizers were continued even though they alone were not sufficient to control the patients' symptoms. Since these agents will be used and should be used in the nervous, irritable individual, it is gratifying to note that Lomotil proved not only effective

*Nilevar, brand of norethandrolone, G. D. Searle & Co.

but also safe in that there was no demonstrable potentiation of the barbiturates or tranquilizing agents.

Safety was further accented by the lack of addiction and withdrawal symptoms. As far as we could determine there was not a single instance of even temporary addiction to the drug. We will, however, continue to pay particular attention to this factor.

We have found that the Lomotil was well tolerated and safe. In selected cases, complete blood and other studies including urinalysis were done prior to and for several weeks after administering Lomotil, without noting adverse manifestations.

In conclusion we wish to state that Lomotil will be of great help in patients with colostomies. We have a number of patients using it now with apparent success in controlling gastrointestinal motility. It is our opinion that the control of colostomies by the use of Lomotil should be gauged by necessity and that the drug should be used on a p.r.n. basis. Smaller dose than 2.5 mg. has been tried as indicated and seemed effective even when used once a day.

Summary

The use of Lomotil in 57 patients with diarrhea of various causes and nature is discussed. Relief of symptoms was excellent to good in 82.4 per cent. The only group in which the drug was considered not effective, as was anticipated, was the group of acute or chronic ulcerative colitis patients. It was well tolerated even in patients with a variety of complications including diabetes. Safety was confirmed by virtual lack of side-effects, no evidence of withdrawal symptoms, no indication of addiction and no demonstrable potentiation of barbiturates. We have found Lomotil to be an excellent drug which is efficacious where other drugs have failed in the management of the various diarrheas.

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Clinicopathological Conference*

from the Philadelphia General Hospital, Philadelphia, Pa.

Dr. William Ehrich (Philadelphia, Pa.)†:—The case which we will present this afternoon is very interesting. I hope that we will all learn something from it.

The protocol which you have before you contains all the information that we had; nothing was added, nothing was subtracted.

Protocol

This 65-year old Italian-born American was first examined at PGH Medical Clinic on 24 July 1959 when he complained of pain and ringing in the ears with diminution of hearing and dizziness; pain in the right shoulder and right anterior chest; difficulty "getting air in" and a brief episode of vomiting. Further history was not obtained nor could other details be elucidated because of language difficulty, although the patient had been in this area since 1921. On examination the patient appeared pale and ill. His weight was 135 pounds. There was smooth prostatic hypertrophy. The chest was slightly increased in AP diameter. No other physical findings were recorded.

Investigations performed at that time were: Hemoglobin, 9.5 gm.; hematocrit, 31 per cent; WBC, 6,200; Urinalysis: specific gravity, 1.027, 10-12 WBC, a few graular casts; VDRL, negative; reticulocyte count, 3.4 per cent; FBS, 109 mg. per cent; BUN, 16 mg. per cent.

A barium series showed an irritable duodenal bulb with a small ulcer crater.

The patient returned on 7 August feeling somewhat improved and at that time was started on antispasmodic and antacid therapy.

He did not return until 20 October at which time he was admitted, following referral by a Health Unit, when a mass in the right chest was discovered on a routine chest film. At this time the patient complained of a one-year history of anorexia and weight loss; a vague history of cough productive of yellowish sputum and a two-week to two-month history of spasmodic cough with hemoptysis associated with right anterior pleuritic pain. Two weeks prior to admission the patient noted the sudden onset of bilateral leg edema which progressively worsened. The patient denied previous illnesses, alcoholism, chills or sweat, or shortness of breath. He stated that he was constipated. It was observed that the

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patient had a poor memory for recent events and the history was considered unreliable.

On examination the temperature was 100° F, pulse 110, respirations 35, blood pressure 150/80 and weight 137 pounds. He was alert and cooperative but appeared somewhat dyspneic at rest, orthopneic, fatigued and somewhat toxic. His skin was pale, his lips slightly cyanotic and his sclerae icteric. He appeared poorly nourished but moderately obese. The chest was slightly increased in AP diameter with dullness to percussion, decreased tactile fremitus and markedly decreased breath sounds over the right lower lung field. There were inspiratory and expiratory wheezes and rhonchi in the right mid lung field but no rales were heard. The heart sounds were distant but the rhythm appeared regular and no murmurs were heard. The abdomen was protuberant. No fluid wave or shifting dullness was elicited. The liver was palpable and smooth with a sharp edge extending almost to the level of the umbilicus. It was questionably tender. The prostate was moderately enlarged and smooth. There was no lymphadenopathy nor jugular venous distention. The lower extremities were massively edematous from above the knees, down and there was moderate presacral edema.

Investigations showed: Hemoglobin, 7.4 gm.; WBC, 5,900; neutrophils, 78 per cent; bands, 46 per cent; segs, 31 per cent; metas, 1 per cent; lymphocytes, 17 per cent; monocytes, 4 per cent; plasma cells, 1 per cent; 1 nucleated RBC/100 WBC. Urinalysis: specific gravity, 1.017; 10-15 WBC; Trace protein. FBS, 94 mg. per cent; BUN, 27 mg. per cent; albumin, 2.6 gm. per cent; globulin, 4.1 gm. per cent; indirect bilirubin, 1.0 mg. per cent; direct bilirubin, 0.5 mg. per cent; thymol turbidity, 4.5; thymol flocculation, 0; cephalin flocculation, 0; alkaline phosphatase, 5.8; PO_4, 5.5; sputum culture: D. pneumonia, strep viridans and Neisseria species; 3 negative smears for acid fast bacteria; circulation time (arm to tongue), 15 seconds; ECG, diffuse flattening of T-waves throughout; chest x-ray, to be shown; skin tests for tuberculosis, histoplasmosis, coccidiomycosis negative.

On the second hospital day fluoroscopy was performed showing a paralyzed right diaphragm at the level of T6, moderate cardiomegaly, increased hilar markings with clear costophrenic angles. It was felt that the density in the right lower lung field represented an elevated diaphragm rather than a pleural effusion.

Repeat fluoroscopy on the following day was reported to show paradoxical or asynchronous movement between the right and left diaphragm, clear bases posteriorly and it was thought on this occasion that the density in the right lower lung field might represent a large globular mass, 15 cm. in diameter, in the right lower lobe area.

The patient was digitalized and given hydrodiuril 50 mg. daily but continued dyspneic and edematous. He remained intermittently febrile with occa-

sional spikes to 102° F, his pulse remained rapid at 110-120 per minute and his cough with hemoptysis persisted.

On the sixth hospital day, 600 c.c. of air were injected into the peritoneal cavity and fluoroscopy repeated in an attempt to visualize the diaphragms without success. A bronchoscopy was performed showing marked narrowing of the right lower lobe bronchus, probably extrinsic, and a biopsy provided insufficient tissue for evaluation.

The following day a Vim-Silverman biopsy of the right chest mass at the anterior axillary line in the 5-6th interspace was performed. A "bony hard" mass was felt and the biopsy showed liver tissue showing congestion and pigmentation of the liver parenchymal cells. A small portal area showed marked fibrosis.

The patient became progressively more toxic with increased dyspnea. A pleural friction rub synchronous with respiration appeared over the pericardial area. Many coarse rhonchi were heard bilaterally and the heart sounds were inaudible.

The patient died on 28 October on the eighth hospital day.

Chest x-rays will be shown.

Our first discussor will be Dr. Charles M. Thompson, our internist.

*Dr. Charles M. Thompson (Philadelphia, Pa.)**:—I first want to look at this problem broadly, then come to some specific items that may help me to make a diagnosis in what appears to be an unusual case.

This is the history of a 65-year old Italian-born American who was in this country 38 years, when in July 1959 he first developed a pain in the right shoulder and chest, respiratory difficulty and vomiting.

The only pointing symptoms at this time are the pain in the right shoulder and the right chest. Now, although pain in the shoulder should suggest diaphragm involvement or irritation by way of the phrenic pathway there still, at this point, is no clear issue on whether the pain originates in the chest, or above the diaphragm or in the abdomen below it.

Three months later this patient went through a health unit and described a cough and expectoration, weakness and anorexia which had been present for one year. A more recent severe cough with hemoptysis and right anterior chest pain, so-called "pleuritic pain" occurred two weeks before. He went to the health unit at the time he noticed the onset of bilateral leg edema.

Notice that in these three months from the original admission of July to October there is no considered or recorded loss of weight.

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Films were taken—Dr. Ostrum will discuss all of these because in my mind there is some confusion as to what these films actually mean and Dr. Ostrum may help us to clear that up.

At this time of admission the physical examination was more fruitful. The patient had fever; he had tachypnea, tachycardia, dysphonia and orthopnea. He was toxic, there was cyanotic icterus.

There were signs at the right base. No rales were heard.

These signs were the type of signs that one might get from compression or invasion of the smaller bronchioles and alveoli. Now in a short period of three months, from July 1959, the liver had reached the umbilicus. It was questionably tender; there was leg edema and now was recorded presacral edema.

There were no signs to suggest congestive failure. There was no venous congestion recorded in the jugular veins; the venous pressure is not recorded and there appears to be at least a normal or high normal circulation time.

At this admission also there were laboratory evidence of anemia, and an active bone marrow responding to either the anemia or to the possible additional stimulation of infection or necrosis.

There was a reversal of the A/G ratio, slight hyperbilirubinemia and modest elevation of the serum alkaline phosphatase.

Numerous studies, fluoroscopic studies and radiographic observations were made. They will be described later by Dr. Ostrum.

A biopsy was done and a bony hard mass apparently was encountered by the very perceptive Vim-Silverman needle. The tissue proved to be liver.

Now at this point I think it's important in our thinking to raise three questions and try to answer them. In my mind these are:

Was the primary condition in the chest or in the abdomen? My feeling at this point is that the primary condition was in the abdomen for reasons that I will cite later.

Second, was the primary condition neoplastic, inflammatory, or cystic with secondary inflammatory changes? I have no way of answering that yet.

Third, was the edema due to heart failure or some other cause or was it due to mechanical factors? I favor mechanical factors here.

Now to discuss in more detail some of the particular symptoms and findings.

I will pass over the head symptoms or findings because they could have resulted perhaps from an infectious process, degenerative changes in the brain; or due possibly to involvement of the brain by some lesion. I do not favor that.

I think the head symptoms are important in that they point up the difficulty in the historical interview. It surely made it difficult to get this history as well as has been recorded here.

The second point; the pain in the right shoulder and anterior chest. Again I say this could have been of abdominal origin as well as the chest. I believe I have seen shoulder pain with anterior chest pain more often with lesions of or around the dome of the liver than with lesions in the lung. Perhaps it's because after all with an expanding lesion of the liver there is less opportunity to spread out; there's more likely to be pressure and impingement on the crus and the phrenic nerve.

Now just before referral back by the health unit the very prominent chest complaints and findings would seem to indicate there was primary pulmonary disease. In the light of the almost precipitous development of liver findings, however, it would seem better to assume at least that they could also represent or they resulted from infradiaphragmatic disease with secondary chest involvement.

The physical findings in the chest, as we have said before, could have resulted from mechanical compression or encroachment. Another finding was the onset of leg edema and later sacral edema. This suggests to me that there could have been blockage of the inferior vena cava by thrombus, tumor invasion or again by encroachment of some sort.

Three months later—that is three months after the patient was first observed —the liver reached the level of the umbilicum and was questionably tender.

To me there are few lesions of the liver that will do this, show such fuminant and rapid enlargement besides primary epithelial neoplasm. These are: florid regenerative hyperplasia as seen in some cases of cirrhosis, or Budd-Chiari's syndrome with endophlebitis of the smaller hepatic veins, the large hepatic veins and their junctional areas with the inferior vena cava. Massive hepatic inflammation may do this.

The second compilation of the laboratory is also before you and I will only comment on a few of these.

The reversal of the A/G ratio is noted here; this certainly suggests a more chronic process than a simple acute one. The mild hyperbilirubinemia and slight increase in the alkaline phosphatase here would go along, of course, with intrinsic pathology in the liver, and might point to a tumor or any other mass of the liver causing intrahepatic cholestasis.

The flattened T-waves would suggest pericardial involvement as with fluid or with thickened pericardium, or degenerative changes.

I'll not attempt to go much further except to make some generalities before I hear from Dr. Ostrum.

My generalities are something like these and I make these with a great deal of care and thoughtfulness.

I think that probably the primary condition is in the liver and involves its coverings or capsule. This condition has been associated with secondary pulmonary changes. The conditions involve the hepatic vein and possibly its junctional area with the inferior vena cava.

My first consideration must be given to primary tumor of the liver that so diffusely involves that organ, the hepatic vein and inferior vena cava, the pleura, lungs and pericardium.

*Dr. L. Kraeer Ferguson (Philadelphia, Pa.)**:—I'm going to be allowed to speak before Dr. Ostrum. I think it's only fair that we both who are on the pan so to speak should have a crack at this before Dr. Ostrum shows us his x-rays.

In the first place this patient was an Italian-born American. I don't know why Dr. Ehrich told us that, but he must have some reason indicating to us that this patient came from abroad and came perhaps from an area that might be different than we might have had here.

I believe that his first complaints, that is of his first admissions or first examination at the clinic, when he had the ringing in his ears and pain and dimunition of hearing and dizziness, are all the result of the anemia which was present, hemoglobin 9.5.

He did, however, have other symptoms which were a little different; those were the pain in his right shoulder and right anterior chest and a difficulty in getting air in. This is put in quotations and it must have been his own way of saying this, but apparently there was a definite difficulty in respiration.

Then he mentions a brief episode of vomiting which apparently was not very prominent.

In this first admission then there weren't very many definite complaints, but the thing that stands out and which was repeated in his second admission was his right shoulder pain and right chest pain and the difficulty getting the air in.

In the investigations that were performed there was nothing much except as Dr. Thompson stated, evidence of bone marrow activity; an increased reticulocyte count and a hematocrit of 31 per cent; his urine showed a few red cells—a few white cells and a few casts which may have been as a result of his slight prostatic hypertrophy.

It is noted that he had a duodenal ulcer or duodenal ulcer crater and an irritable duodenal bulb—I agree with Dr. Thompson that it is probably put in here as a sort of a red herring because—certainly none of his other symptoms

*Professor and Chairman, Department of Surgery, Graduate School of Medicine, University of Pennsylvania.

are compatible with this finding. Nothing that he says—nothing that is talked about in here except perhaps the brief episode of vomiting, could be pinned onto a symptom which might be looked upon as an ulcer symptom.

Then he was all right for two months or at least we have no data about him—until he came in to the health clinic with a mass in his right chest which was discovered there apparently accidentally. But on further questioning he had trouble for a long time, anorexia and weight loss, and he had had a yellowish sputum which about two weeks ago or perhaps two months ago they weren't quite sure, apparently changed so that he had spasmodic cough with hemoptysis associated with his right anterior pleuritic pain.

This suggests to me that whatever is going on had become more marked and it sounds a little as though something was draining into his bronchi which produced an increased amount of fluid which had to be coughed up and which also had perhaps produced some ulceration because of the hemoptysis that is present.

Then he said that two weeks prior to admission there was a sudden onset of bilateral leg edema which got worse. I agree with Dr. Thompson that this bilateral edema certainly can't be of cardiac origin. There must be some sort of a lesion which has produced a thrombosis of his vena cava in the region of the liver or just above the diaphragm.

This is one thing that I would feel certain about and in addition there are other factors that would make one feel that this might well be a thrombosis that is above the diaphragm because in further history one sees that there is a paralysis of the diaphragm on the right side indicating that the right phrenic nerve is probably involved in some inflammatory process, perhaps the same one which is producing the phlebitis of his vena cava.

Now there are some other things that are important in this story now. The patient is febrile; he has a temperature of 100° F; his pulse is up and his respiration is up indicating that there is some evidence of inflammation someplace, something has gone on which was present not in the early part of his disease.

Furthermore he is very markedly dyspneic and orthopneic even at rest so that he's having some respiratory difficulties which are more than the ordinary and more than he's had. In addition, his sclerae are icteric.

This certainly would indicate that there is some bile pigment being absorbed into the blood stream.

Now when we come to examine the chest one finds that it is dull with decreased tactile fremitus and decreased breath sounds in the right lower lung fields. In other words in this area there is something which is not transmitting air, which doesn't even transmit fremitus, which must then be fluid of some sort which is present in this lower part of his lung.

In the middle lung he has inspiratory and expiratory wheezes and rhonchi which means then that the large air passages are being pressed upon and that there is a partial obstruction and as the air passes through it rhonchi are heard.

I agree with Dr. Thompson that there is no evidence of any cardiac difficulty here. At least his heartbeats were normal—the rhythm was normal and although no murmurs were heard, there was no fluid or shifting dullness in the abdomen indicating that there is no ascites. The liver was palpable and enlarged down as far as the umbilicus. So that something is going on in the liver to make this enlargement.

The lack of jugular venous distention indicates also that there is no cardiac decompensation or at least not markedly so.

The fact that he has a very massive edema of the lower legs and also presacral edema indicates first that he may have what we said was a thrombosis of the vena cava but also he has probably a protein deficit which may also add to that edema and give him some of his other symptoms.

His blood picture is surely one of marked anemia and of marked activity of the bone marrow which is indicative perhaps of toxemia which has been going on apparently in this patient for some time.

The toxemia is one to which the patient can't respond very well. He had a marked shift to the left of his neutrophils, but only 5,900 white cells indicating that this patient isn't quite able to respond to quite an overwhelming difficulty.

He had only a slight increase in his bilirubin perhaps, but it's definite and certainly his liver function changes are not marked.

Therefore, we find that this patient must have some lesion of his liver pressing up into his chest, but it isn't producing a marked difficulty in the liver itself.

As we go on we find that on fluoroscopy he has a paralyzed right diaphragm which I said probably indicates a paralysis due to pressure on the phrenic nerve of his right side. The other thing that's important and interesting is that, although he has this great big shadow in his right lung, he has a clear costophrenic angle indicating to me that he doesn't have a pleuritic type of inflammation because with a pleurisy or pleuritic reaction one would expect this costaphrenic angle to have fluid in it.

As we go on we find that he has a paradoxical movement of his diaphragm which is just another way of saying he has a paralysis of his diaphragm; the bases are clear posteriorly which also indicates that this is not a generalized involvement of his lower lung, but it's one of definite local involvement.

This apparently is borne out by the fact that he has a 15 cm. mass in the lower right lung area.

Now it's apparent that all of these findings were probably infective or at least were producing some local inflammation inside this mass. He had a temperature of 102 indicating he was having absorption and an elevation of his pulse rate and his cough with bloody sputum persisted indicating that this mass was doing something in his lung which was producing an ulceration and which was producing bleeding.

The bronchoscopy showed a narrowing of his right lower lobe bronchus with extrinsic pressure indicating then that there's something pressing into the area of his bronchus rather than involving the bronchus itself.

Finally, the finding that when they attempted to do a biopsy by using the Vim-Silverman needle they found a bony hard mass. I'm sure that this description of a bony hard mass would not probably be that way if it didn't mean exactly what it said, a bony hard mass. In other words, I take it that there is a calcification, that the needle came into something that was calcified but from which liver tissue was obtained. Therefore it's apparent that this mass, whatever it was, arose from the liver and pushed the diaphragm up rather than arising in the chest. This we know because the needle was inserted in the fifth or sixth interspace; that is it was way up here in the anterior axillary line where the needle was put in. In other words then the mass was up there and liver was there; the liver then is probably the thing that's in the chest rather than something in the chest pushing down on the liver.

He later developed a peripleural friction rub in the pericardial area and finally died on his eighth day.

It is my idea that this patient probably had some sort of a parasitic disease, perhaps echinococcic cyst, which developed before he came to this country. As you all know, these cysts become rather large; the larvae die and the cyst persists often without any symptoms until infection takes place. They often calcify and to stick my neck out I'll say that this is probably a case of echinococcic cyst of the liver arising into the chest, perforating into a bronchus.

Now there's one factor in this that doesn't quite ring true and that is that there's no eosinophilia in this patient. This I believe can be explained on the basis that the larvae are dead in the cysts and therefore the eosinophilic reaction which normally obtains in the blood, does not occur or had disappeared by the time this patient came for his trouble.

Now I'd like to see the x-rays.

*Dr. Herman W. Ostrum (Philadelphia, Pa.)**:—I think my colleagues are expecting a lot of me, and I am afraid I will have to disappoint them.

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*Professor of Radiology, University of Pennsylvania School of Medicine; Professor of Radiology, Graduate School of Medicine, University of Pennsylvania.

Some of the films in this case have been removed, and you will have to take my word for their interpretation. On 28 July 1959, an x-ray examination was made of the upper gastrointestinal tract. Most of the films are missing, but I do have a one-hour study that showed a normal stomach, normal mucosa and a duodenal cap that showed some scarring but no active ulceration. Peristalsis and motility were normal. The liver was somewhat enlarged. The next day, 29 July, another examination of the upper gastrointesinal tract was made with the use of Hypaque. The patient had not been prepared carefully, and in such cases of poor preparation and food retention, Hypaque will offer more than the ordinary barium study. It will show an ulcer crater better than barium will. This study was also negative.

Fig. 1

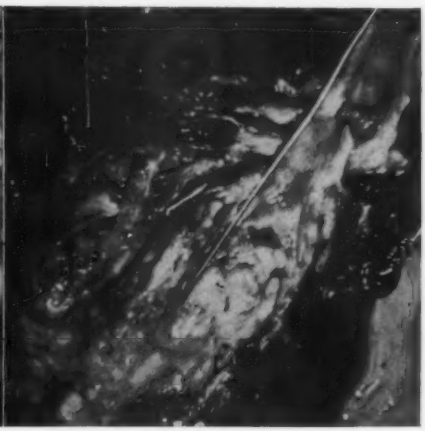

Fig. 2

Fig. 1—The amebic abscess is in the liver extending into the right pleural cavity.
Fig. 2—Extension of the abscess into the lower lobe of the right lung.

During the fluoroscopic study it was noted that the right diaphragm was elevated and its motion very much restricted. Seriographic films of this area showed the right diaphragm elevated with a small radiolucent area beneath the diaphragm, suggesting abscess formation.

Three months later, on 21 October, a study of the chest revealed a normal left lung, an irregular density occupying the lower portion of the right lung. The upper margin of this density was irregular in outline and there was considerable pleural thickening in the involved area. There was density in the right costophrenic angle. The heart was not enlarged or displaced. The irregular density in the right base offered a problem in differential diagnosis. Was it a tumor in the lung? Was it infection in the lung due to atelectasis caused by bronchogenic carcinoma? Was it a localized area of suppuration and pneumonitis? My impression is that this was most likely a localized inflammatory process

of pulmonary suppuration, pneumonitis and pleuritis, the cause of which I do not know.

To summarize: A study of the upper gastrointestinal tract showed some scarring of the duodenal cap but no other lesion. A study of the chest three months later revealed a localized, inflammatory process in the right base, the cause of which was undetermined.

Dr. Thompson:—I will make my conclusive remarks, getting some aid, of course, from Dr. Ostrum, but still pretty well sticking to the line that I previously had set for myself.

I feel that this is a lesion that has involved liver parenchyma and the chest symptoms are secondary to involvement there.

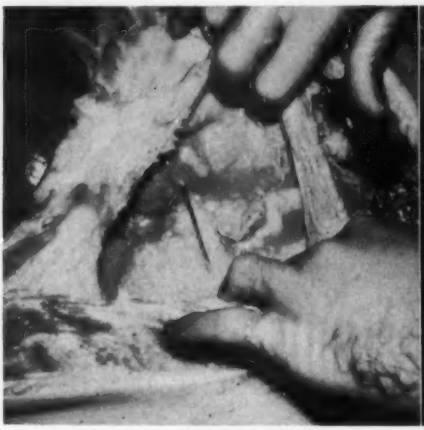

Fig. 3

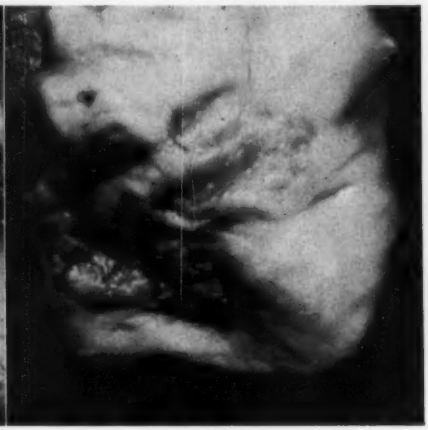

Fig. 4

Fig. 3—Extension of the abscess into the pericardium.
Fig. 4—Amebic ulcers in the cecum.

The massive sudden enlargement of the liver and presacral and dependent edema suggest to me inflammatory disease or tumor invasion of the hepatic veins and/or the vena cava.

I must give particular consideration—and I did as Dr. Ferguson did—to the possibility of echinococcus disease even though the interval is long, 38 years, from living in a country where we would expect echinococcus disease and even though he had no eosinophilia because only about 25 per cent of cases of echinococcus disease have any eosinophilia.

I gave primary consideration, therefore, to echinococcus disease and/or a tumor within the liver; in this case with invasion of the lung and pericardium

and thrombosis of the hepatic vein and the junctional areas of the vena cava and/or a thrombophilic tendency.

The evidences for infection do not dissuade me from the possibility of this still being a primary epithelial tumor because after all these tumors notoriously break down and become necrotic and often present as infective processes.

The appearance of a cavity area in the lung without calcification makes me a little concerned about what was one of my first diagnoses, echinococcus disease. I would expect some calcification here.

So, in again not taking all my clues from Dr. Ostrum I hold for infrahepatic process with infection. I still think there is a primary disease of the liver; that it is tumor or cystic and that inflammatory involvement is secondary to this.

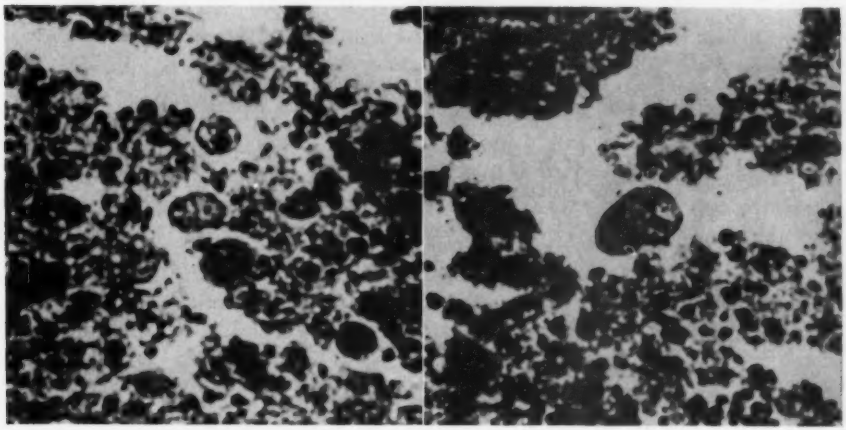

Fig. 5 Fig. 6

Figs. 5 and 6—Amebae in pus of the liver abscess.

Dr. Ferguson:—Dr. Ehrich, I don't think I have very much more to add to what Dr. Thompson has said.

I feel as he does that this is a primary hepatic disease with secondary involvement of the super riding lung; exactly the type of disease, I think you'll have to tell us. It certainly seems to me though that it must be something that has to do with necrosis and suppuration which is now well walled off and which is beginning to drain into a bronchus and is giving enough absorption to produce a very toxic individual.

Dr. Ehrich:—Our two discussors came very close to the correct interpretation of this case.

The autopsy revealed that there was an empyema in the right pleural cavity that contained 750 c.c. of pus.

Figure 1 shows you the empyema; it was filled with greenish-whitish pus-like material. The cavity was bordered on one side by diaphragm and liver tissue; on the other side by lung; and on a third side by the pericardium of the heart.

After the purulent material was removed it was found that there were three openings from the empyema cavity; one opening about three cm. wide extended down into the liver. It ended in an abscess that measured four cm. in diameter and contained a shaggy, bloody material.

Another opening led from the empyema cavity up into the right lung.

In the lung it ended again in an abscess (Fig. 2). This measured perhaps three cm. in diameter. It contained a similar shaggy bloody material as in the liver. There was a communication of the abscess right with a major bronchus of the lower lobe which explains why the patient brought up a yellow sputum once in a while. The communication is shown by a probe.

The third opening led from the empyema to the pericardium.

When this was opened it was found that it contained approximately 1,000 c.c. of a purulent sanguineous fluid. Figure 3 shows the communication, with the empyema. Please notice the small sprout which passes through the opening into the empyema cavity.

We have then an abscess primarily apparently of the liver that perforated into the pleural cavity, causing the production of an emypema which then perforated into the lung and finally into the pericardial sac. The heart itself was perfectly normal.

Another significant finding in this patient is shown in Figure 4.

This shows a portion of the cecum and ascending colon. There were present, as you can see, shallow ulcers covered with an insignificant amount of debris all the way from the ileocecal valve up to the hepatic flexure. There were no other ulcers in the intestinal tract.

These gross observations, to be sure, suggest very strongly that we are dealing here with a case of amebiasis with extension from the intestines to the liver and subsequent perforation into the pleural and pericardial cavities.

The proof for this suggestion was found by the microscope.

Figure 5 shows a portion of the pus that was found in the liver. Please notice that most of the small cells are pus cells, but the large elements are typical ameba.

In Figure 6 you see the ameba even better. Notice the classical picture of a living active ameba.

We may say then that we have here a patient with amebiasis who did not have diarrhea or dysentery at any time that we know of.

It is well known that in areas like Philadelphia amebiasis does not usually cause dysentery, that is the discharge of mucus, blood and necrotic parts of the mucosa. If there is any intestinal disturbance in areas like Philadelphia this will most likely be a diarrhea. But in about 20 per cent of the cases we have constipation instead. As you may have noticed, our patient had constipation.

In spite of the absence of dysentery or diarrhea a good many patients develop liver abscesses. It is rather typical for these abscesses to perforate through the diaphragm into the pleural cavity and it is equally typical for the empyema if it develops to perforate into the lungs and into the pericardial sac.

The lesson to be remembered is the fact that amebiasis may be silent clinically in that there is no dysentery or diarrhea.

President's Message

At the meeting of the Board of Trustees in Milwaukee on 16 April, Dr. Robert R. Bartunek, Chairman of the Program Committee, presented a resume of what he and his committee are planning for the Annual Meeting and Postgraduate Course. On Tuesday afternoon, 24 October, they are planning a series of round tables, each of which will be staffed by experts. It will be possible to go from table to table during the session and spend as much time as one desires at each.

As part of the Postgraduate Course, on Saturday, 28 October, the final session will be devoted to an X-ray Classroom. Here there will be prepared questions and the experts will answer them. There will also be instructional demonstrations and an opportunity for questions and answers.

Both of these types of sessions are new to our meetings and I am sure that they will do much to stimulate interest in the convention and the Postgraduate Course. Regardless of how fine the program is, it requires the fullest cooperation from our membership to help it succeed. I sincerely hope that you will attend the Cleveland Convention and that you will actively participate in the fine programs which are being arranged for you.

Henry Baker

THE American Journal OF Gastroenterology

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NEWS NOTES

26th ANNUAL CONVENTION
AMERICAN COLLEGE OF GASTROENTEROLOGY

Sheraton-Cleveland
Cleveland, Ohio
22-25 October 1961

The Cleveland Chapter of the American College of Gastroenterology guarantees you, regardless of the weather outside, a warm glow in their hospitality rooms, Mezzanine 1 and 3 at the Sheraton-Cleveland.

Plan to meet your fellow members there! Consult the hotel Bulletin Board on your arrival.

Twenty-sixth Annual Convention

A feature of our Twenty-sixth Annual Convention in Cleveland, Ohio, this October will be a series of round table discussions on pertinent topics. This was announced by the Chairman of the Program Committee, Dr. Robert A. Bartunek. There will be approximately 23 tables, each staffed by three panelists, who are specialists in their field and there will be an opportunity afforded to spend time at several of the tables.

These round tables will be part of the afternoon session on Tuesday, 24 October 1961 and will be under the direction of Dr. Stanley S. Sidenberg.

The two sessions on Wednesday 25 October will be devoted entirely to Liver Disease. There will be individual papers presented on various topics on Monday as well as Tuesday morning.

Course in Postgraduate Gastroenterology

The Annual Course in Postgraduate Gastroenterology of the American College of Gastroenterology will be given at the Sheraton-Cleveland Hotel in Cleveland, Ohio, on Thursday, Friday and Saturday, 26, 27, 28 October 1961.

This year, the last session on Saturday afternoon will be devoted to an x-ray class presented by an outstanding panel of specialists who will answer questions and present instructional demonstrations. There will be ample opportunity afforded for individual questions and answers.

The sessions on Thursday afternoon will be held at the Cleveland Clinic and on Friday night, there will be a joint session with the Cleveland Academy of Medicine. The speaker at that time will be Dr. H. Marvin Pollard of Ann Arbor, Mich.

The Course will be given by a distinguished faculty, selected from the Medical schools in Cleveland and the surrounding areas. It will be open only to those who have matriculated and paid the registration fee, which is $35.00 for those affiliated with the College and $50.00 for nonmembers.

Further details and applications may be obtained from the Executive Director, American College of Gastroenterology, 33 West 60th St., New York 23, N. Y.

Fellowship Keys

Keys for *Fellows* of the American College of Gastroenterology have been authorized by the Board of Trustees. An illustration of the key is at the left.

These may be ordered from the headquarters office, 33 West 60th Street, New York 23, N. Y., at $10.00 each including federal tax and shipping charges.

The reverse side of the key will be engraved with your name and the date of your election to Fellowship. Send your order today.

ABSTRACTS FOR GASTROENTEROLOGISTS

GASTROINTESTINAL TRACT

FIVE DUODENAL ULCERS IN A SIBSHIP: T. H. Almond. Brit. M. J. 5133:1332 (23 May), 1959.

The increased incidence of peptic ulceration within families is discussed. This may be due to environmental factors, similar eating habits, smoking habits, drinking habits and blood groups.

In a large family consisting of a mother and 15 children, four brothers and one sister developed duodenal ulceration. All cases came to surgery and were improved by this treatment.

A determined effort to find common factors in this family revealed that aside from all having blood groups A, Rh positive and at some time or other being engaged in a driving occupation, there were no obvious common causative agents.

STANLEY STARK

HEREDITARY HEMORRHAGIC TELANGIECTASIA: Chalmers H. Davidson. Scottish M. J. 4:260 (May), 1959.

This paper reports the record of a family with hereditary hemorrhagic telangiectasia extending over seven generations. The disease is familial and may be transmitted by either sex as a Mendelian dominant. There is no abnormality in the platelets or clotting mechanism, and the lesion is essentially a capillary defect. The naevi may be nodular or of the spider variety and are commonly found in the skin and mucous membranes of the nose, mouth, lungs and gastrointestinal tract. There is no specific treatment.

LOUIS A. ROSENBLUM

ESOPHAGUS

ENDOSCOPY (CONCLUDED): Edward B. Benedict. New England J. Med. 260:535 (12 Mar.), 1959.

The author discusses endoscopic progress.

Esophageal strictures caused by lye and other corrosive substances can now be prevented by early administration of cortisone which deters fibroplasia. Webs of the esophagus may occur with anemia (Plummer-Vinson syndrome) or without anemia, benign mucous-membrane pemphigus, thyroid diseases and esophageal diverticula.

Achalasia (cardiospasm) of the esophagus is caused by the destruction of the intramural plexus. One of the causes in Brazil is Chaga's disease, in which the neurotoxin set free from dead *Trypanosoma cruzi* destroys

the vegetative ganglion cells of hollow muscular organs. A rare complication is aorto-esophageal fistula with hemorrhage. The author favors cardiotomy (Heller operation) plus pyloroplasty. Carcinoma of the esophagus occurs 6 times more commonly in peptic stenosis, 22 times more in corrosive stricture, 91 times more in esophageal webs and 7 times more in achalasia, than in the general population.

The author found by periodic esophagoscopic examinations that portocaval shunt proved far more effective in reducing portal pressure and esophageal varices than did splenorenal shunt.

Biopsy is dangerous in cases of tumors located submucosally. The only justification for biopsy is an ulcerated or suspicious mucosa or a truly intraluminal tumor.

In squamous cell carcinoma of the esophagus, the x-ray is remarkably accurate but in about 2 per cent of cases with suspicious symptoms, lesions were revealed by esophagoscopy.

In suspected cases of nonopaque foreign bodies the use of iodized oil only, for x-ray visualization and immediate esophagoscopy with general anesthesia is recommended.

Esophagoscopy was helpful in the diagnosis of compression due to *arteria lusoria*, an anomalous form of the right subclavian artery; also in hypertrophy of cricopharyngeus muscle and tuberculosis of the esophagus.

As to gastric endoscopy, the author discusses the newer instruments in the offing, namely the fiberscope, the Tomenius aspiration biopsy, the combination gastroscope-biopsy instrument (Benedict and others) and the endoscopic-photographic units. Biopsy has helped greatly in the clarification in the diagnosis of gastritis.

The author would eliminate the terms "superficial" and "hypertrophic" gastritis and "chronic gastritis" and retain the expression "gastric atrophy". Early esophagoscopy and gastroscopy is recommended in most cases of upper gastrointestinal bleeding. The author makes a plea for the revival of interest and training and use of peritoneoscopy which would eliminate the necessity of major surgery in many cases.

Palmer and Wirts surveyed gastroscopic and esophagoscopic accidents in 267,175 gastroscopies and 40,540 esophagoscopies by 890 endoscopists. Perforation was the main problem and anesthetic reaction was not an inconsiderable threat. The over all accident rate was 0.79 per cent in cases of gastroscopy and 0.25 per cent in cases of esophagoscopy.

SAUL A. SCHWARTZ

STOMACH

GASTRECTOMY IN THE TREATMENT OF DUODENAL ULCER: Edwin L. Brackney, Harold S. Stubbs, Thomas Mann, Connor C. Dyess and William H. Moretz. J. M. A. Georgia 48:402 (Aug.), 1959.

This is a description of the details of a study of various methods of treatment for peptic ulcer of the duodenum now being conducted at the Medical College of Georgia. An attempt is being made to compare objectively the results of four of the currently popular surgical procedures used in the treatment of duodenal ulcer. A preliminary report of the results to date has been presented but as yet there is not a sufficiently large number of cases in any of the series to give any statistically significant report of the results. With the information so far obtained however, it would seem that the least desirable of the four procedures under study is the Billroth I, since four out of 14 patients with this type procedure have had recurrent ulcers.

JACOB A. RIESE

BLEEDING DUODENAL ULCER: Martin Bandler and J. A. Desjardins. J.A.M.A. 170:2174 (29 Aug.), 1959.

A series of 162 consecutive cases of bleeding duodenal ulcer was studied to relate the course of abdominal pain to the severity of bleeding. Statistics revealed that the continued presence of exaggeration of pain was associated with minimal bleeding, whereas relief of pain was more characteristic of moderate and severe hemorrhage.

Hematemesis by itself was not found to be a clear-cut indication of severe bleeding. Syncope, on the other hand, commonly heralded a massive hemorrhage. A history of previous hemorrhage was of no apparent value in predicting the severity of bleeding from duodenal ulcer. The proportion of the number of severe hemorrhages to the total number of cases for a given decade increased progressively with advancing age. There appeared to be an increased frequency in the incidence of blood group O among patients with bleeding duodenal ulcer. An increased occurrence and severity of bleeding in the fall and winter months was also noted.

LOUIS A. ROSENBLUM

INTESTINES

PNEUMATOSIS CYSTOIDES INTESTINORUM HOMINIS—PART II: Jacob Reichert. Am. J. Proct. 10:264 (Aug.), 1959.

Gas cysts of the intestinal tract are comparatively rare and usually difficult of diagnosis. Finney described the first case occurring in the United States during 1908, but gave no pathogenesis. Today no definite cause can be ascribed.

However, investigation seems to point to increased lymphatic pressure as a probable reason for the development of these blebs, that contain carbon dioxide and oxygen.

The increased pressure traps these gases soon after they enter the lymphatic system.

Normally the low and almost negative pressure of the lymphatics as they enter the blood stream with a moderate pressure at the source move the lymph along with fair speed, but increased tension at the source due to depletion of essential metabolites,

electrolytes with deficient protein, predisposes to lymph stagnation, increased tension and "budding" of the lymph channels with trapped gas contents.

No simple remedial technic can be instituted, but correction of the altered metabolic processes and a readjustment of malnutritional status often reduced the pressure in the lymphatics with a disappearance of the cyst formation.

J. EDWARD BROWN

CONGENITAL DUODENAL ATRESIA AND STENOSIS: D. R. Smith. New Zealand M. J. 58:514 (Aug.), 1959.

Congenital atresia or stenosis of the duodenom occurs at a rate of 1/20,000. Surprising is the high proportion of mongols among the cases reviewed in the literature amounting to up to 30 per cent. While duodenal atresia presents a striking syndrome requiring immediate surgery shortly after the child is born, duodenal stenosis shows less marked symptoms and investigation may be delayed for years.

The author reviews four cases of his own, one of atresia and three of stenosis. His x-ray reproductions are most instructive.

WALTER CANE

PANCREAS

ACUTE PANCREATITIS IN PATIENTS RECEIVING CHLOROTHIAZIDE: D. H. Johnston and A. L. Cornish. J.A.M.A. 170:2054 (22 Aug.), 1959.

Acute pancreatitis was observed in three women, 50 years of age or older (in a year's period), who had been taking 0.5 to 1.0 gm. of chlorothiazide daily for several months, and in an 84-year old man taking 1 gm. once or twice a week for 15 months, in the course of treatment for cardiovascular disease. In no case was there a history of gallbladder disease, alcoholism, or other predisposing conditions. The diagnosis was based on clinical and laboratory studies and was confirmed in one case by autopsy. Although the specific etiology remained undetermined chlorothiazide was considered as a possible cause. All had severe heart disease. The authors wish to alert physicians to the possibility of chlorothiazide being responsible.

ERNEST LEHMAN

PSYCHOSOMATIC MEDICINE

BACKGROUND OF FUNCTIONAL DISORDERS OF THE GASTROINTESTINAL TRACT: Oscar K. Diamond. Am. J. Proct. 10:331 (Oct.), 1959.

In this article the author reviews the history of psychosomatic illness from the days of the ancient Greeks through the present era of modern psychiatry.

He classifies patients with psychiatric disorders into three categories:

1. Those with physical symptoms without bodily disease as a cause.
2. Those with a physical disease whose original causative factors were emotional.
3. Those with organic disease but whose symptoms arise from mental factors.

In the final portion of the paper the author explains the physiological changes associated with emotional reactions.

THEODORE COHEN

FUNCTIONAL DISORDERS OF THE MOUTH AND ESOPHAGUS: James A. Brice. Am. J. Proct. 10:336 (Oct.), 1959.

The role of oral and esophageal disease as related to psychosomatic illness is reviewed.

Hunger, glossodynia, Simmon's disease, bulemia, cardiospasm and other esophageal neurosis are explained as the psychiatrist sees them.

THEODORE COHEN

NEUROLOGY OF THE GASTROINTESTINAL TRACT: John R. Whittier. Am. J. Proct. 10:340 (Oct.), 1959.

A rather thorough review of the neurology of the gastrointestinal tract is presented.

The author feels that the response of any segment of the gastrointestinal tract at any time is given neural determination not only by immediate context but by the history of the organism. In terms of this concept much of psychiatric diagnosis and to a great extent the structure of psychotherapeutic treatment can be explained.

The goal of behavior is survival of the organism and misinterpretation of this goal by the neural system because of unconscious associations of present context with past experience is the basis for gastrointestinal behavior other than digestion, absorption and excretion.

THEODORE COHEN

FUNCTIONAL DISORDERS OF THE STOMACH, GALLBLADDER AND PANCREAS: Paul J. Tomlinson. Am. J. Proct. 10:346 (Oct.), 1959.

In this paper a number of psychosomatic disorders of the stomach and gallbladder are discussed. These include nervous stomach, gastric neurosis, ulcer syndrome, gallbladder disease and diabetes.

The author shows how chronic emotional problems lead to organic visceral impairment. He suggests that early therapy might reverse the process and relieve the symptoms. Where indicated medical or surgical treatment must also be utilized concomitantly.

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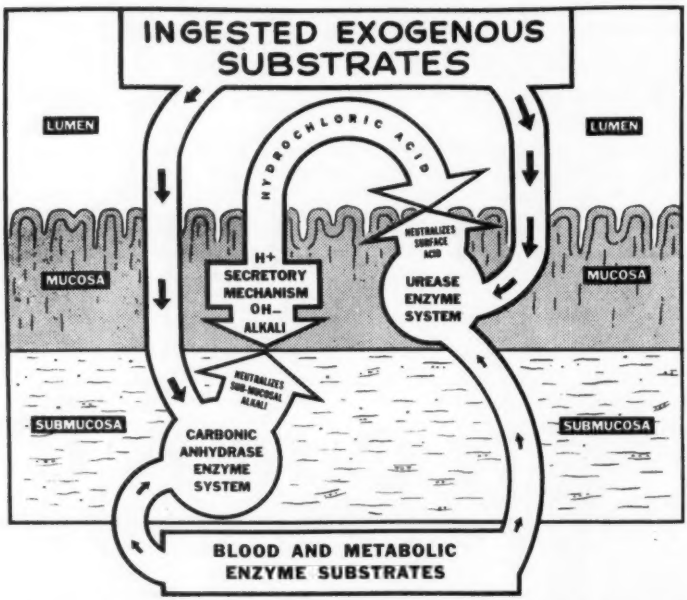

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DOSAGE:
One packet T.I.D. after mealtime and one packet at bedtime.

REFERENCES:

(1) Goodfriend, Vanderkleed & Goodfriend. "Enzymatic Therapy of Peptic Ulcer and Digestive Disorders." American Journal Gastroenterology, Vol. 33, No. 1, Pgs. 80-89, January 1960.

(2) Kelly, H. T., M. D., "Treatment of Gastroduodenal Ulcer and Certain Digestive Disorders with Mucosal Enzyme Substances", American Journal of Gastro., Vol. 33, No. 12, December, 1960.

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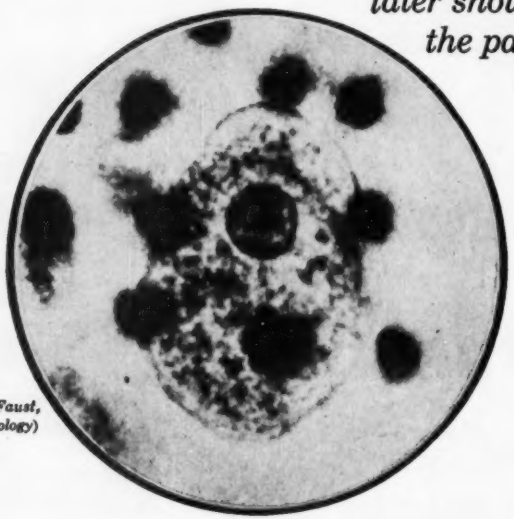

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1. Frye, W.W., and Lampert, R.: Treatment of Asymptomatic Endamoeba histolytica Carriers with a Formulation of Bacitracin-Methylene Disalicylate and Iodochlorhydroxyquin (Anameba). Am. J. Gastroenterol. **34**:429-432 (Oct.), 1960.

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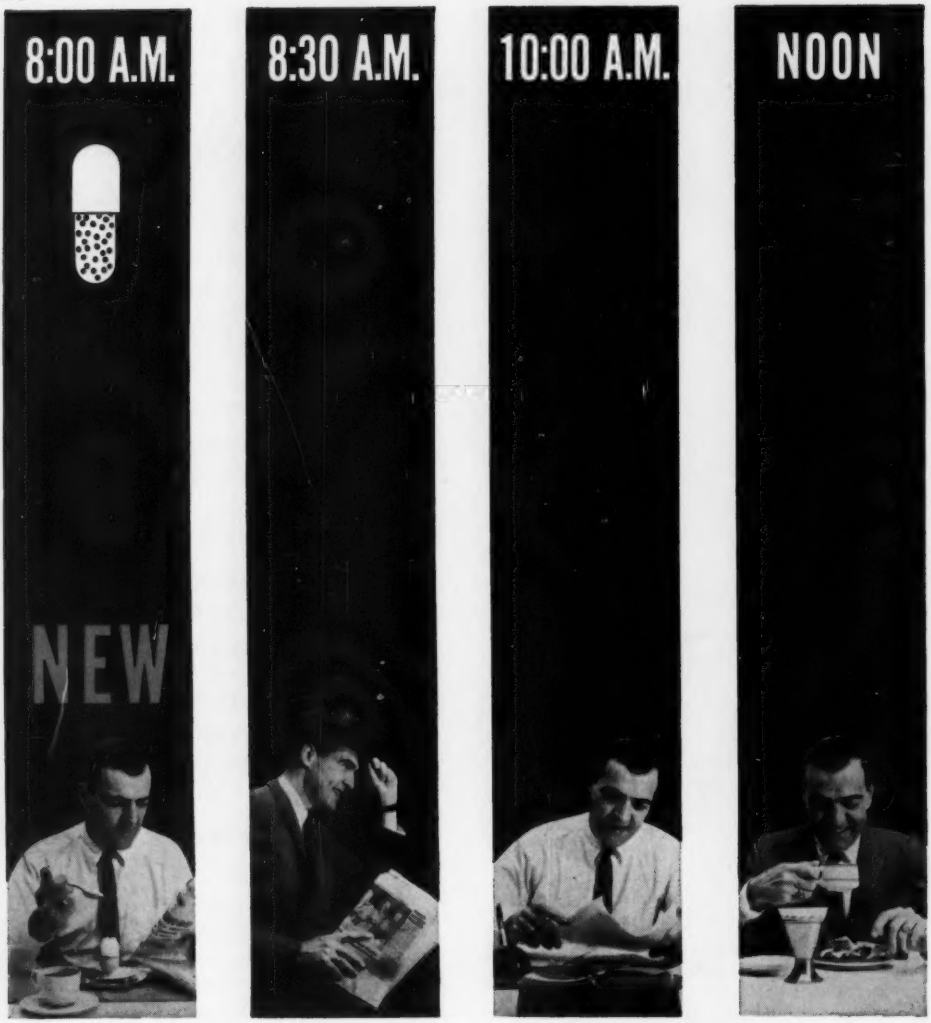

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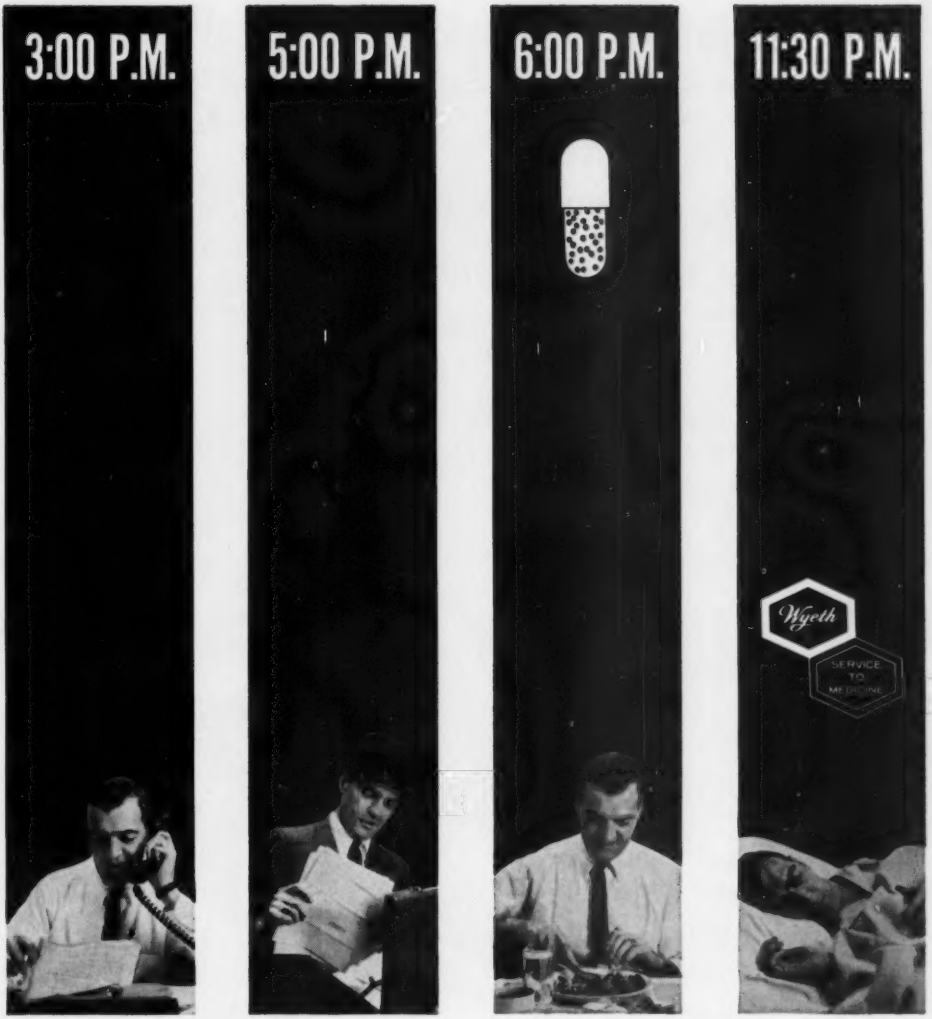

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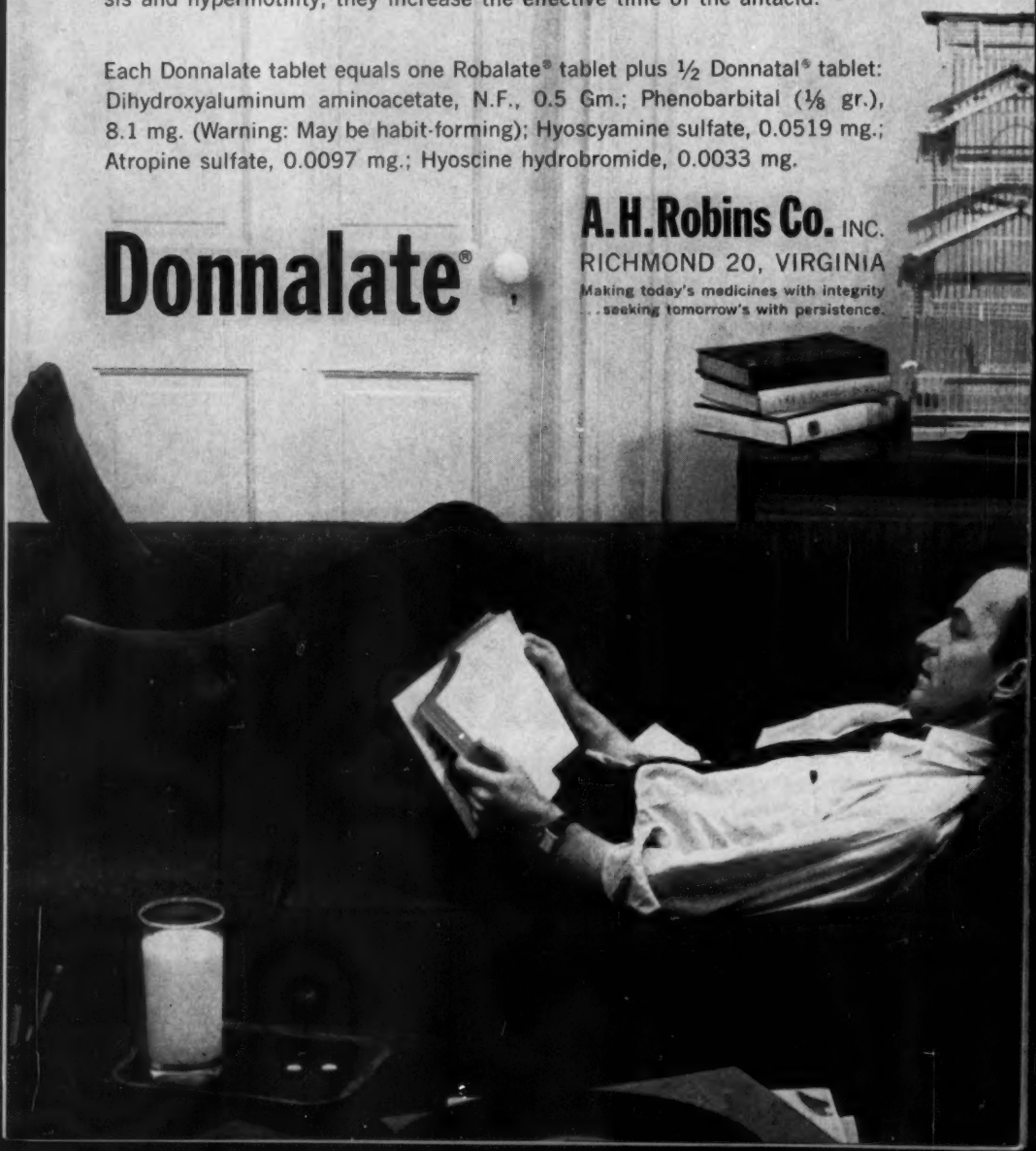

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1. Weiss, J.: Amer. J. Gastroent., July 1960.
2. Breidenbach, L. and Secor, S. M.: Amer. J. Surg., Jan. 1957.

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References: (1) Rider, J. A.; Moeller, H. C., and Lee, J.: Am. J. Gastroenterol. *32*:714, 1959. (2) Modern Drug Encyclopedia and Therapeutic Index, ed. 6, New York, Drug Publications, Inc., 1965, p. 281. (3) Kleckner, M. S., Jr.: J. Louisiana M. Soc. *108*:359, 1956. (4) Kleckner, M. S., Jr.: Clin. Res. Proc. *5*:19, 1957. (5) Riese, J. A.: Am. J. Gastroenterol. *28*:541, 1957.

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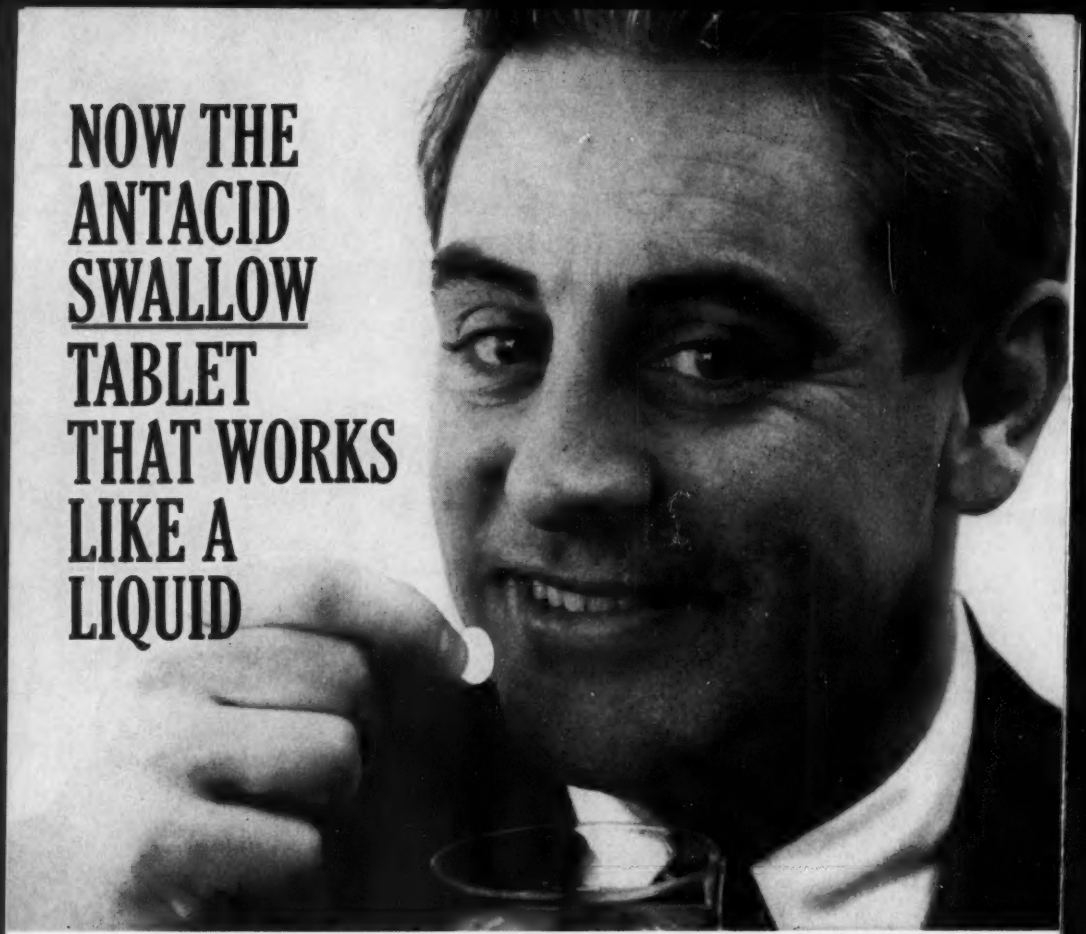

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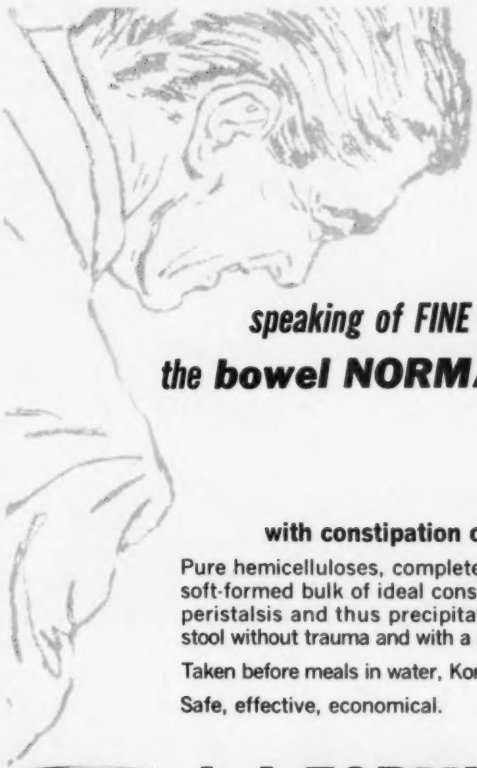

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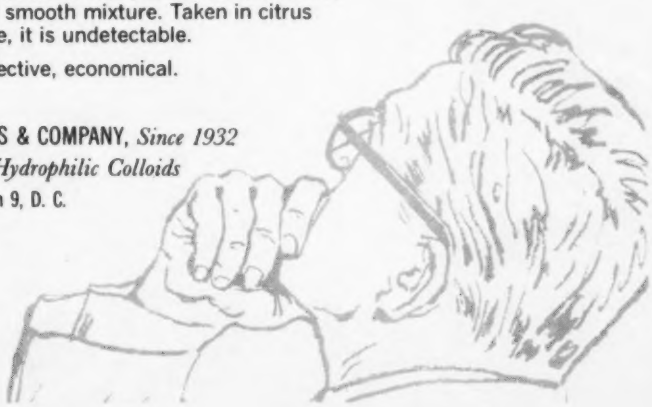

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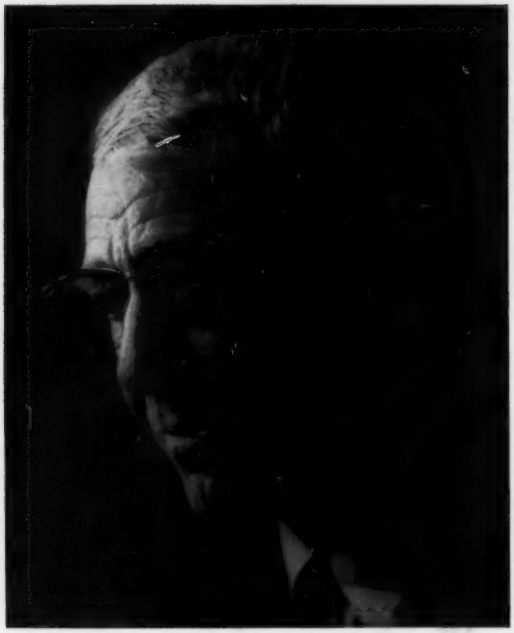

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1. Beil, A. R. and Brevetti, R. E.: Management of constipation during the puerperium, New York State J. Med. 60:2706-2707, September 1, 1960.
2. McCarthy, E. V.: Calcium bis-(dioctyl sulfosuccinate) in treatment of constipation, Clin. Med. 7:2257-2259, November, 1960.

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